scientific literature pertaining to this issue. In the absence of a *weight of evidence approach* that is based upon scientifically rigorous *weight of evidence guidelines*, it is not at all clear what criteria were used to evaluate the relationship between LPT and lung function. In my opinion, this is a significant scientific deficiency in the DRAFT Quality Review Report report and needs clarification by the EPA Scientific Advisory Board.

The sole purpose of this report is to provide the EPA Scientific Advisory Board with objective evidence, expert professional commentary and recommendations regarding the conflicting scientific literature, considerable scientific uncertainty and doubtful clinical significance pertaining to the relationship between isolated asbestos-related LPT (pleural plaques) and lung function at the present time. In this regard, I have no personal, professional, or financial conflicts of interest in this matter. My sole intent is to help insure that the *full body* of currently available scientific and medical evidence is carefully considered in addressing this issue, consistent with my passionate belief that all public policy related to environmental health effects should be based upon sound and rigorous science. In my opinion the EPA Scientific Advisory Board has a responsibility to avoid overstating the relationship between asbestos-related LPT (pleural plaques) and lung function, and instead should take the current state of confusing uncertainty as a "golden opportunity" to bring scientific clarity to the issue through an independent, scientifically rigorous *weight of evidence* assessment. I strongly recommend that it do so prior to issuing a final report on its *Quality Review of the EPA Draft Assessment entitled Toxicological Review of Libby Amphibole Asbestos (August 2011).*

CRITICAL ASSESSMENT OF THE LITERATURE CITED IN THE SAB REPORT

The Scientific Advisory Board cites seventeen published reports to support its assertion that "LPT is associated with reduced lung function". In my professional opinion, this body of cited literature does not provide a sufficient degree of definitive, scientifically rigorous evidence to support this broadly-stated conclusion. My critical assessment of these reports, and reasons why I believe they do not sufficiently support this conclusion, are provided below.

Lilis, et al (1991). [7] This report shows a dose-related relationship with a decrease in FVC alone and the extent of both circumscribed pleural fibrosis and diffuse pleural fibrosis on chest radiographs. It is assumed that the term circumscribed pleural fibrosis pertains to the older term for LPT as defined in the 1980 ILO classification. While the methodology of this report is sound considering the data that was available to the investigators, there are multiple limitations to this study. First of all, a pleural index score for circumscribed pleural fibrosis was determined from chest radiographs, which are less accurate than high resolution CT scans in estimating the extent of pleural thickening and less accurate in distinguishing pleural fibrosis from pleural fat. Secondly, FVC alone is the only lung function parameter reported. In the absence of the FEV1, the FEV1/FVC ratio and lung volumes, the reduced FVC could suggest either restrictive or obstructive ventilatory impairment. Furthermore, smoking was not controlled by pleural index score. This is important, since it is possible that the reported reduction in FVC with increasing pleural index score could, possibly, be related to chronic obstructive lung disease from smoking and not be related to circumscribed pleural fibrosis. Furthermore, the study was not controlled for body mass index (BMI). Therefore, it is also possible the reported reduction in FVC could, possibly, be related to increased body mass. *Thus, while the results of this study are suggestive of a relationship between the pleural index score and a reduction in FVC, they are by no means definitive of a direct relationship and do not establish circumscribed pleural fibrosis as the cause of the FVC reduction.*

Paris et al (2009). [8] The stated objective of this study was to describe the relationships between asbestos exposure and pleural plaques [LPT] and asbestosis in a large cohort of formerly exposed asbestos workers, and to assess asbestos exposure parameters linked to the presence of HCRT [high resolution computed tomography] of these two diseases by means of multivariate analysis. This study demonstrated "strong relationships between asbestos exposure and the presences of pleural plaques [LPT] and, to a lesser extent, between asbestos exposure and asbestosis." The presence of pleural plaques [LPT] was associated with time since first exposure and cumulative exposure index. The presence of asbestosis was associated with cumulative exposure index. The duration of exposure was not associated with either pleural

plaques [LPT] or asbestosis. Although the methodology used in this study was sound, the authors themselves properly state that this study has a number of limitations. Most importantly, however, the SAB Report cites this publication as supporting the assertion that there is a "relationship between LPT and lung function." However, *lung function was not, in any way, investigated in this study. It is purely an imaging assessment and has nothing to do with lung function. Therefore, in no way does this study support the SAB assertion that there is a "relationship between LPT and lung function."* Indeed, it is very puzzling why the SAB would cite this publication in support of that assertion.

Clin, et al (2011). [9] The objective of this study was to analyze the relationship between isolated pleural plaques [LPT] confirmed by CT scanning and lung function in subjects with occupational exposure to asbestos. This is a well-designed and well executed study. The results show that isolated parietal and/or diaphragmatic pleural plaques [LPT] are associated with a *slight reduction* in total lung capacity (TLC) among subjects with pleural plaques [LPT], with these subjects having a TLC of 98.1% predicted in comparison to a TLC of 101.2% predicted in subjects free of pleural plaques [LPT] at a p-value that barely meets statistical significance ($p = 0.0494$). The authors also report a forced vital capacity of 96.6% predicted among subjects with pleural plaques [LPT] in comparison to 100.4% in subjects free of pleural plaques [LPT] ($p < 0.001$) and a forced expiratory volume in one second (FEV1) of 97.9% predicted among subjects with pleural plaques [LPT] in comparison to 101.9% predicted in subjects free of pleural plaques [LPT] ($p = 0.0032$). The authors conclude that there is a *trend* toward a "restrictive pattern" among individuals with isolated and/or diaphragmatic pleural plaques [LPT], although *"the observed decrease in FVC and TLC is unlikely to be of real clinical significance for the majority of subjects studied." Indeed, from a clinical perspective, both the TLC and FVC of subjects with pleural plaques are not abnormal – they are both well within the normal range.* It is also important to point out that the proportional decrease in FVC is greater than the proportional decrease in the TLC among subjects with pleural plaques [LPT]. Since TLC is the "gold standard" for assessing restrictive ventilatory impairment, this suggests the possibility that FVC alone, as used in the Lilis study, may not be a reliable parameter for assessing restrictive ventilatory

impairment in subjects with pleural plaques [LPT]. Although the methodology used in this study is sound, the authors acknowledge several limitations, such as the subjects not being representative of the general population exposed to asbestos, possible selection bias with respect to subjects that had been previously diagnosed with asbestos exposure-related diseases and the possibility of a "healthy worker effect." It is certainly possible that any or all of these limitations could account for the very slight decrease of TLC observed among subjects with pleural plaques [LPT]. *Thus, not only is it unlikely that the observed results are of real clinical significance, it is also possible that the very slight difference in the TLC between subjects with and without pleural plaques [LPT] is the result of inherent statistical errors related to the limitations acknowledged by the authors.*

ATS Official Statement (2004). [10] The American Thoracic Society (ATS) Official Statement on the Diagnosis and Initial Management of Nonmalignant Diseases Related to Asbestos states that "studies of large cohorts have shown that a significant reduction in lung function attributable to the plaques, averaging about 5% reduction in FVC, even when interstitial fibrosis (asbestosis) is absent radiographically. Three references are cited in support of this statement; all three references use FVC alone (not TLC) as the measurement of lung function and chest radiographs (not CT scans) for the determination of pleural plaques [LPT]. However, the ATS Official Statement also states that *"This has not been a consistent finding and longitudinal studies have not shown a more rapid decrement in pulmonary function in subjects with pleural plaques."* Three references are also provided in support of this statement. In this regard, the report also states that *"Decrements, when they occur, are probably related to early subclinical fibrosis"* - that is, early subclinical *lung parenchyma fibrosis* and *not LPT*. In addition, while the report cites two references that show a significant but small association between the extent of circumscribed pleural plaques and FVC, the authors conclude with the statement that *"most people with pleural plaques have well preserved lung function."* They cite one reference that used CT scans to determine the presence of pleural plaques [LPT] which showed no effect on lung function related to pleural plaques [LPT]. *Thus, this comprehensive report objectively cites some of the conflicting study results that have appeared in the medical literature and, in my*

opinion, does not provide a sufficient weight of evidence to unequivocally assert that pleural plaques [LPT] in and of themselves are universally or typically associated with a decrement in lung function. Indeed, it is the expert opinion of the report authors that decrements, when they do occur, are probably related to early subclinical lung parenchyma fibrosis and not to LPT, per se.

Ohlson, et al (1984). [11] The stated objectives of this study were compare the lung function of long-term asbestos cement workers without asbestosis to a reference group and to elucidate the possible impact of pleural plaques on lung function. The presence of pleural plaques [LPT] was determined by chest radiography. This study, which was well-controlled for smoking, showed that there was a statistically, but probably not clinically, significant decrease in both FEV1 and FVC among workers exposed to asbestos cement dust after adjustment for age, height, tracheal area and smoking history. *There were no significant differences in lung function between those with and without pleural plaques [LPT].* The authors conclude that that the group exposed to asbestos cement dust had a minor impairment in lung function, that this was mainly due to obstructive changes [not restrictive changes], that the lung function changes were probably not clinically significant and that there were no significant differences in lung function between asbestos-exposed workers with and without pleural plaques [LPT]. Thus, the results of this study do not support an assertion that pleural plaques, in and of themselves, are associated with a decrement of lung function. *The results of this study also raise the possibility that studies which have used FVC as the only lung function parameter in investigating the effect of pleural plaques (such as the previously cited Lilis study), could have shown a decrement in FVC that was due to obstructive changes (due to dust, smoking or some other exposure), with the decrement in FVC being unrelated to the presence of pleural plaques [LPT].*

Ohlson, et al (1985). [12] This was a four year follow-up study of ventilatory function in former asbestos cement workers to determine whether a there was any decline in lung function in the four year period, to assess the relationship between pleural plaques [LPT] and ventilatory function and to examine the comparability of cross-sectionally predicted versus longitudinally

determined changes after four years. The presence of pleural plaques [LPT] was determined by chest radiography. The main result of this study was a progressive decrease in FEV1 and FVC during four years, with the group that had the highest exposure losing 8% of the FEV1 and 9% of the FVC and the group with the lowest exposure losing 5% of the FEV1 and 5% of the FVC. Thus, there was a progression of *obstructive ventilatory impairment* during the four year follow-up period, with the greatest decline in FEV1 and FVC occurring among former workers who had the highest asbestos exposure. Consistent with the results of the previously reported Ohlson, et al study, *this study showed that pleural plaques [LPT] had no effect on the decline in lung function.* Since this was a longitudinal study, it shows that the presence of pleural plaques [LPT] had no effect on the decline in lung function over a four year time period. The authors opine that the observed obstructive pattern could be explained by the aerodynamic properties of the dust generated from the handling and trimming of asbestos cement products. *Again, however, the longitudinal obstructive decline lung function was unrelated to the presence of pleural plaques [LPT].*

Jarvolm and Sanden (1986). [13] The objective of this study was to determine whether individuals with pleural plaques [LPT] have impaired respiratory function, compared with individuals with similar asbestos exposure but without pleural plaques [LPT]. The study cohort consisted of non-smoking, male, asbestos-exposed shipyard workers. The presence of pleural plaques [LPT] was determined by chest radiography. The study results showed that subjects with pleural plaques [LPT] had lower FEV1 and lower FVC than subjects without pleural plaques [LPT] and that these differences were statistically significant. The decrease in FEV1 appeared to less than the FVC, suggesting a mild restrictive process. In general the FVC was about 5% lower in subjects with pleural plaques [LPT] than in subjects without pleural plaques [LPT]. The study also showed that the average differences in FVC between subjects with and without pleural plaques [LPT] were 3.4% for men with low asbestos exposure and 8.2% for men with high asbestos exposure. The FVC difference for men with low asbestos exposure was not statistically significant; the FVC difference for men with high asbestos exposure was statistically significant. The majority of FVC values for all subjects were within the normal range, however

3% of men without pleural plaques [LPT] and 16% of men with pleural plaques [LPT] had an FVC below the lower limit of normal. Based upon these results the authors conclude that *"pleural plaques are associated with slightly impaired lung function."* However, the authors do not assert that pleural plaques [LPT] are the cause of the slightly impaired lung function. They state that the low sensitivity of chest radiographs to detect pleural plaques [LPT] makes it probable that several cases of plagues were undetected and that "This would also mean that it was difficult to detect an effect associated with plaques." Furthermore, the authors carefully point out that *"it is improbable that pleural plaques themselves decrease lung volume merely by their size"* and *"a few small pleural plaques cannot reduce chest mobility by 5-10%."* They go on to state that *"another possible hypothesis the existence of subradiographic fibrosis associated with the plaques."* They also state that *"This hypothesis is supported by the finding that the difference in FVC between men with and without pleural plaques is only significant for the heavily exposed men." This implies that it is that it is unlikely that pleural plaques [LPT] in and of themselves are the cause of the lower FVC observed in subjects with pleural plaques, rather it seems more likely that the lower FVC in these subjects is caused by lung parenchyma fibrosis that is not detectable by chest radiograph.*

Hjortsberg, et al (1988). [14] The objective of this study was to investigate the pattern of changes in lung function cased by asbestos and the additive effect of smoking in asbestos-exposed subjects with pleural plaques. This study was not designed to assess the effect of pleural plaques [LPT] on lung function in asbestos-exposed individuals. *Since the reference group (control group) in this study consisted of healthy non-smoking men without a history of asbestos exposure, the results of this study cannot be used to make any inference about the effect of asbestos-related pleural plaques [LPT] on lung function.* Chest radiographs were used to determine the presence of pleural plaques in asbestos-exposed subjects. Stepwise logistic regression analysis was used to assess pulmonary function data for the ability to predict whether subjects belong to the asbestos-exposed group. The results of this study do suggest that vital capacity (VC) is the most sensitive lung function parameter for discriminating between asbestos-exposed subjects and non-exposed subjects and that smoking does not have any

influence on the VC. The authors also demonstrate that there is no statistically significant difference in diffusion capacity among smokers, ex-smokers and non-smokers in the asbestos-exposed group. Once again, however, *the results of this study cannot be used to conclude that there is any reduction in lung function between asbestos-exposed subjects with and without pleural plaques.*

Oliver, et al (1988). [15] The objective of this study was to investigate the association between asbestos-related pleural plaques [LPT] and lung function in a group of workers occupationally exposed to asbestos. Chest radiographs were used to determine the presence of pleural plaques [LPT]. The study results show a statistically significant inverse relationship between FVC% predicted and the level of diagnostic certainty (none, suspect, definite) among subjects with pleural plaques]LPT], however in all cases the reported FVC% predicted was in the normal range (> 80% predicted). There was no such relationship between FEV1 and the diagnostic certainty of pleural plaques [LPT]. In this regard, pleural plaques [LPT] were associated with a restrictive pattern, however this association, although statistically significant, was relatively small (4.3 percentage points) and was not very strong ($p = 0.0431$). In this regard, it is important to note that when age and height were taken into account, there was a statistically significant difference in both FVC and FEV1 between groups with and without pleural plaques, suggesting that obstruction could, possibly, be contributing to the observed difference in FVC. In a univariate logistic regression analysis, the prevalence of dyspnea was higher in the group with pleural plaques (39.5% vs 26.6%, $p = 0.025$), however in a multivariate analysis there was no correlation between dyspnea and pleural plaques [LPT] or the extent of pleural plaques [LPT] by level of certainty, when controlling for asbestos exposure and smoking. Also of importance is the finding that that there was no association between single breath carbon monoxide diffusing capacity (DLCO) and either pleural plaques or the suggestion of a restrictive ventilatory phenomenon by FVC. However, there was a statistically significant difference in DLCO among subjects who had both pleural plaques and an FVC suggestive of restriction. The authors state that this finding suggests that the DLCO reduction in this group was related to the presence of interstitial fibrosis that was not present on chest radiograph and not necessarily to

the presence of pleural plaques [LPT] per se. *They further state that the clinical significance of the observed 4.3 % decrement in FVC among subjects with pleural plaques is uncertain and that "the presence of both pleural plaques and restriction may be a marker of radiographically occult interstitial fibrosis in asbestos-exposed populations." The authors make no assertion that the observed decrement in FVC is caused by pleural plaques [LPT], per se.*

Borbeau, et al (1990). [16] The objective of this study was to investigate whether asbestos-related pleural abnormality and isolated pleural plaques [LPT] are associated with respiratory impairment independently of parenchymal abnormality. Chest radiographs were use to detect the presence of pleural abnormalities and pleural plaques [LPT]. Lung parenchymal abnormality was determined by gallium-67 uptake measured 48 hours after a 4 microcurie injection. Results showed that subjects with isolated pleural plaques had a 200 ml decrease in FEV1 and a 350 ml decrease in FVC in comparison without pleural plaques, after adjusting for age, height, smoking, and parenchymal disease by quantitative gallium-67 uptake, and that these differences were statistically significant ($p < 0.05$). However, there was no demonstrable difference in most cardiorespiratory measurements on sub-maximal and maximal exercise between subjects with and without pleural plaques [LPT]. Based upon these results the authors conclude that it *is possible* that isolated pleural plaques [LPT] are associated with significant reductions in spirometric lung volumes independently of radiographic or subradiographic asbestos-related parenchymal lung disease. However, they do not state that there is a direct causal relationship between pleural plaques [LPT] and a reduction in spirometric lung volumes. *Indeed, in view of the relatively small differences in FEV1 and FVC between subjects with and without pleural plaques and the absence of significant differences in cardiorespiratory measurements on exercise, the authors are careful to state that "This supports the clinical opinion that pleural plaques are little more than a sign of asbestos exposure."*

Schwartz, et al (1990). [17] The objective of this study was to determine whether pleural fibrosis is associated with diminished lung volumes and, if so, whether the two of pleural fibrosis (circumscribed pleural plaques versus diffuse pleural thickening) is a determinant of the

extent of pulmonary impairment. The presence of circumscribed pleural plaques [LPT], diffuse pleural thickening and interstitial fibrosis were determined by chest radiographs. The results of this study showed that subjects with circumscribed pleural plaques [LPT] had a mean decline in FVC of 140 ml (90.3% predicted) and those with diffuse pleural thickening had a mean decline of 270 ml (almost twice as great as subjects with circumscribed pleural plaques [LPT]) (85.7% predicted) in comparison to asbestos-exposed subjects without circumscribed pleural plaques [LPT] or pleural thickening (94.7% predicted); these differences were statistically significant. In all cases the FVC values remained in the normal range. For each category of pleural fibrosis (none, circumscribed pleural plaques [LPT] and diffuse pleural thickening) the observed FVC was lower for those with radiographically apparent interstitial fibrosis than for those without radiographically apparent interstitial fibrosis. Among subjects with concurrent interstitial fibrosis, there was a consistent decline in the FVC% predicted that was significantly associated with the type of pleural fibrosis: none = 83.3% predicted, circumscribed pleural plaques = 80.1% predicted, and diffuse pleural thickening = 73.6% predicted. Thus, asbestos-exposed workers with radiographically normal parenchyma as well as those with radiographically-apparent interstitial fibrosis were found to have a similar, independent relationship between the presence and type of pleural fibrosis and decrements in FVC. However, *the authors state that, because asbestos-exposed workers with pleural fibrosis have more extensive exposure histories than those with normal pleura, it is quite possible that that they are also more likely to have parenchymal fibrosis.* It is also well know that chest radiographs are not particularly accurate in quantitating the extent of parenchymal fibrosis. In this regard, *the authors state that it is possible that for each ILO grade of radiologically-apparent parenchymal fibrosis, those with pleural fibrosis have more parenccymal fibrosis than those with normal pleura*. They also state that *"it is difficult to conceive that that pleural plaques, in and of themselves, result in the abnormal chest wall motion that accounts for the observed decrements in FVC."* Finally, the authors state that *"We are therefore led to speculate that subclinical alveolitis or interstitial fibrosis not detected by routine chest radiograms is responsible for the development of restrictive lung function among those with asbestos-induced pleural fibrosis." That is, they do*

not directly attribute the observed lung function abnormalities to the presence of pleural plaques [LPT], per se.

Miller, et al (1992). [18] The objective of this study was to assess the relationship between pulmonary function to radiographic interstitial fibrosis in a large cohort of 2,611 asbestos-exposed insulators, with and without pleural abnormalities. This is a comprehensive, well-designed study of a large number of asbestos-exposed individuals. The results showed a statistically significant inverse relationship between FVC and the ILO profusion score on chest radiographs (as a measure of interstitial fibrosis), with a stepwise decrease in FVC with increasing score, except for the intermediate scores of 1/2 and 2/1, which were no different from each other. Of note is the fact that workers with a profusion score of 0/0 (i.e. no radiographic evidence of interstitial fibrosis) had an FVC that was lower than expected (88.0% predicted). The authors indicate that the lower than expected FVC was most likely the result of interstitial fibrosis that was not detectable on chest radiographs, citing a previous study which showed that 18% of patients with histological evidence of interstitial fibrosis had no interstitial fibrosis detectable on chest radiographs. Study results also showed that that 56% of study subjects had pleural thickening, with 83% of these subjects having circumscribed pleural thickening [LPT] and 17% of these subjects having diffuse pleural thickening. Subjects with circumscribed pleural thickening [LPT] had a mean FVC of 82.4% predicted and subjects with diffuse pleural thickening had a mean FVC of 69.0% predicted in comparison to subjects with no pleural thickening, who had a mean FVC of 88.9% predicted. Thus, this study demonstrates that diffuse pleural thickening is associated with a greater diminution of FVC than circumscribed pleural thickening. It also demonstrates that the FVC in subjects with circumscribed pleural thickening [LPT] is significantly lower than the FVC in subjects without circumscribed pleural thickening at all profusion scores for radiographic interstitial fibrosis, including a profusion score of 0/0 in which there is no radiographic evidence of interstitial fibrosis. As noted in previously cited publications, it is highly unlikely that the decrement in FVC observed in subjects with circumscribed pleural thickening [LPT] is related to restrictive movement of the chest wall. However, *the observed decrement FVC in subjects with circumscribed pleural thickening [LPT]*

and a profusion score of 0/0 (i.e. the absence of radiographically detectable interstitial fibrosis) is consistent with the possibility that the observed FVC decrement is related to subradiographic interstitial fibrosis, as suggested in several previously cited studies, and not to the circumscribed pleural thickening [LPT], per se.

Van Cleemput, et al (2001). [19] The objectives of this study were to investigate the relationship of the measured size of pleural plaques to estimated asbestos exposure and to investigate the possible relationship of plaque size and pulmonary function. High resolution CT scans of the chest were used to detect the presence of pleural plaques [LPT] and to measure the size of the pleural plaques. This was a well-designed study that has the advantage of using high resolution CT scans for the assessment of pleural plaques [LPT], which enabled the investigators to exclude potential confounding factors, such as diffuse pleural thickening and subradiographic interstitial fibrosis, which may not have been apparent in studies that used chest radiographs alone for the assessment of pleural plaques [LPT]. Thus, they were able to better isolate any effects of pleural plaques themselves more accurately than studies that used chest radiographs. In my opinion, this is the best and most definitive study on the relationship of pleural plaques [LPT] to lung function that has been published to date. Pleural plaques were detected in 70% of asbestos-exposed subjects and none were detected in control subjects who were not exposed to asbestos. Neither interstitial fibrosis nor diffuse pleural thickening was evident on high resolution CT scans of asbestos-exposed subjects. Study results showed that there was no relationship between pleural plaque [LPT] surface area and cumulative asbestos exposure, time since first exposure, or smoking history. Furthermore, *neither the presence nor the extent of pleural plaques was correlated with lung function parameters. Specifically, there was no statistically significant difference in vital capacity (VC), FEV1, the FEV1/FVC ratio, measurements of airflow, or diffusion capacity between asbestos-exposed subjects with pleural plaques [LPT] and asbestos-exposed subjects without pleural plaques determined by high resolution chest CT scans.*

Miller (2002). [20] This is a short *letter to the editor* submitted to the *American Journal of Respiratory and Critical Care Medicine*, in response to the study of Van Cleemput, et al, which was discussed above. In this letter, the author congratulates Van Cleemput, et al, for using high resolution CT scans to quantitate the extent of asbestos-related pleural plaques and to estimate associations with asbestos exposure with lung function. However, he appears to be critical of the Van Cleemput, et al, study, by stating that it is difficult to relate one variable, such as pleural plaques, to another, such as pulmonary function, when the spectrum of each variable is limited. In this regard, he is confirming a well-known, inherent difficulty in conducting such studies. He indicates that not reporting the "degree of pleural plaques" on chest radiographs, in accordance with the criteria of the 1980 International Labour Office Classification of Radiographs (1980 ILO Classification) is a matter of concern. He briefly reports the main results of three other studies that did use the 1980 ILO Classification that showed conflicting results. He then offers the opinion that "It must be concluded that when sufficient numbers of workers with a sufficient extent of PP [pleural plaques] are analyzed, there is a significant effect on pulmonary function attributed to PP [pleural plaques]." *The opinion of the author is respected, although it does not in any way effect the scientific rigor of the Van Cleemput, et al, study or the validity of the results obtained.* First of all, it should be noted that at the time of the Van Cleemput publication in 2001, the 1980 ILO Classification was obsolete, having been replaced by the 2000 ILO Classification. Secondly, the methodology used by Van Cleemput, et al, to determine the surface area (extent) of pleural plaques [LPT] on high resolution CT scans of the chest is significantly more accurate than determining the extent of pleural plaques [LPT] on chest radiographs using the 1980 ILO Classification. Thirdly, the number of subjects in the Van Cleemput study provides more than enough statistical power to achieve a high degree of statistical significance in study results. Fourthly, as pointed out in the response to this letter from the article authors, their study included pleural plaques whose size (surface area) was representative of the average case, and that very large pleural plaques are neither common nor representative. *Thus, I concur with the response from the article authors in concluding that the comments in this letter do not invalidate their observation that there was no effect of pleural plaques [LPT] on pulmonary function, not even a trend.*

Whitehouse (2004). [21] The objective of this study was to assess the incidence and extent of pleural-related changes and the longitudinal loss of lung function associated with tremolite exposure from the vermiculite mining and processing activity in Libby, Montana. Initial chest radiographs were used to assess the presence and extent of pleural changes . Repeated measures of covariance were used to statistically assess pulmonary function over time, with time-modeled linearity. This is an *excellent, straight-forward study* that is well-designed to investigate the stated objectives. It specifically pertains to tremolite exposure from vermiculite mining and processing in Libby, Montana, and takes into account smoking history and body mass index (BMI). Of 123 subjects studied, 67 (55%) had pleural changes only, consisting of either pleural plaques [LPT] or diffuse pleural thickening. That is, *both pleural plaques and diffuse pleural thickening were included in determining whether or not pleural changes were present on initial chest radiographs.* The remaining 56 subjects (45%) had both pleural changes and minimal radiographic evidence of interstitial changes. Study results show that the total group of 123 subjects showed an average, statistically significant, yearly loss of 2.2% in FVC, 2.3% in TLC and 3.0% in DLCO over a period of 35 months. For the 67 subjects with pleural changes alone on initial chest radiographs, there was an average, statistically significant, yearly loss of 2.2% in FVC, 2.9% in TLC and 2.9% in DLCO over a period of 35 months. In this regard, the authors opine that "it would appear that tremolite-actinolite-richerite-winchite amphibole found in Libby vermiculite has a propensity for causing pleural changes that result in a progressive restrictive pattern on pulmonary function testing," implying that Libby vermiculite could have lung function effects that are different from other forms of asbestos. *However, this study showed no statistically significant correlation between the extent of pleural changes on chest radiograph and the loss of pulmonary function.* Furthermore, this study was not designed to specifically investigate the effect of pleural plaques [LPT] on the loss of lung function, and *does not demonstrate that pleural plaques [LPT], per se, are associated with a loss of lung function*. In this regard, the authors demonstrated that *"the only clearly discernible event leading to accelerated loss of pulmonary function in the entire group was benign asbestos related pleural effusions."* They also state that *"Pleural changes alone are unlikely to cause a*

decrease in DLCO" and that *"DLCO decreases are likely to be associated with interstitial disease not apparent clinically on either plain chest radiograph or HRCT."*

Sichletidis, et al (2006). [22] The objective of this study was to evaluate the progression of radiologic findings as well as the progression in respiratory function among asbestos-exposed individuals in Northern Greece, 15 years after initial evaluation. Chest radiographs were used to assess the presence, extent and progression of radiologic findings. The results of this study showed that, during the 15 year period between 1988 and 2003, the mean surface area of pleural plaques among 126 subjects increased from 8.52 ± 11.4 cm^2 to 17.18 ± 19.24 cm^2. However, the authors do not report the statistical significance of this difference in plaque surface area and, in view of the large standard deviations in plaques surface area, statistical significance is doubtful. This is a major limitation. Furthermore, the authors provide no explicit information on exposure cessation. That is, we do not know if, or when, exposure cessation occurred during the 15 year interval period. This is another major limitation. The authors report a statistically significant decrease in both TLC and FVC during the 15 year interval. However, only 18 out of the 126 subjects (14%) had pulmonary function tests performed. Thus, it is questionable whether this small sample is representative of the group of 126 as a whole. This is another major limitation. Finally, among the 18 subjects who had pulmonary function tests, the authors report a statistically significant, but weak, negative correlation between expansion in plaque surface area and TLC ($r = -0.486$, $p = 0.041$). Again, it is questionable whether this change in TLC among 18 subjects is representative of the group of 126 subjects as a whole. Furthermore, the coefficient of determination is very weak ($r^2 = 0.236$), indicating that the observed decrease in TLC is primarily due to factors other than the expansion in plaque surface area. *In general, in my opinion, this is a poorly designed, very weak study with multiple significant scientific limitations. In this regard, cannot be used to make any scientifically valid or acceptable inference about the relationship between pleural plaques [LPT] and lung function.*

Wilken, et al (2011). [23] This study is a systematic review and meta-analysis of the results of 30 peer-reviewed publications, consisting of 9,921 asbestos-exposed workers. The objectives

of this study were to identify and quantify alterations of lung function parameters in subjects occupationally exposed to asbestos, as well as to assess whether or not occupational exposure to asbestos leads to impairment in lung function independently from the non-malignant radiological findings of pleural fibrosis and asbestosis (interstitial fibrosis). Of significance is the fact that *both* pleural plaques [LPT] and diffuse pleural thickening were considered together as a *single entity* in the assessment of pleural fibrosis; *that is pleural plaques [LPT] was not considered as a separate entity in the assessment of pleural fibrosis*. This study systematically collected detailed information from the studies reviewed and used robust methods of statistical analysis to assess relationships between lung function and non-malignant radiographic findings reported in the reviewed studies. Based upon a meta-analytical analysis of FVC, FEV1 and the FEV1/FVC ratio, the results of this study showed that asbestos exposure is associated with both restrictive and obstructive ventilatory impairment and that, even in the absence of radiological parenchymal or pleural fibrosis there is a trend for functional impairment. That is, impairment in lung function clearly exists among asbestos-exposed subjects, however lung function impairment occurs *"either with or without asbestos-related radiographic abnormalities."* With respect to forced vital capacity (FVC), study results show that FVC impairment occurred in workers without radiographic evidence of either asbestos-related parenchymal or pleural abnormalities, that the impairment in FVC was most pronounced in subjects with radiographic evidence of asbestosis (86.5% predicted, 95% CI = 83.7 - 89.4% predicted), that subjects with pleural fibrosis had a significantly less degree of FVC impairment (89.0% predicted, 95% CI = 86.5 – 91.5% predicted), that subjects with normal radiographic imaging had the least amount of FVC impairment (95.7% predicted, 95% CI = 93.9 – 97.3% predicted), that FVC was significantly lower in all three radiological sub-groups among studies using chest radiographs compared with those using high resolution chest CT scans, and that FVC was significantly lower in the normal imaging and pleural fibrosis radiographic sub-groups in which more than 25% of the subjects were never smokers. The study did not take into account differences in body mass index (BMI) among subjects in different subgroups. In view of study results that show that functional impairment occurs either with or without radiographic abnormalities and the fact that both pleural plaques [LPT] and diffuse pleural thickening were both included in the pleural

fibrosis radiographic subgroup, *no inference can be made about the lung function effects of pleural plaques [LPT], per se. That is, this study does not demonstrate any direct effect of asbestos-related pleural plaques [LPT] on a reduction in lung function.*

CONCLUSIONS

Based upon my extensive, objective review of the medical and scientific literature that addresses the relationship between asbestos-related localized pleural thickening and lung function, as well my objective critical review of the literature cited by the EPA Scientific Advisory Board to support its assertion that "LPT is associated with reduced lung function" in its DRAFT Quality Review Report, I have reached the following conclusions:

1. There is a large body of conflicting and inconclusive peer-reviewed scientific literature regarding the relationship between asbestos-related localized pleural thickening and lung function. In this regard, there is considerable uncertainty about the scientific validity of any assertion that "LPT is associated with reduced lung function." Further rigorous scientific evaluation is necessary before the EPA Scientific Advisory Board can make this assertion with any acceptable degree of scientific certainty.

2. There is no *weight of evidence* study, based upon scientifically rigorous *weight of evidence guidelines*, to support the assertion of the EPA Scientific Advisory Board that "LPT is associated with reduced lung function." Thus, it is not clear exactly what scientific criteria the EPA Scientific Advisory Board used to support this statement.

3. The body of literature cited in the DRAFT Quality Review Report to support the assertion that "LPT is associated with reduced lung function" does not provide a definitive, scientifically rigorous basis for making such an assertion. Indeed, one cited publication does not even address the relationship between LPT and lung function and one cited publication is a letter to the editor regarding another cited publication without consideration of the scientifically robust response from the authors.

4. In its DRAFT Quality Review Report, the EPA Scientific Advisory Board did not consider, or even mention, the results of a robust, peer-reviewed Delphi Study that was published as the *American College of Chest Physicians Consensus Statement on the Respiratory Health Effects of Asbestos* in the journal *CHEST* [4] in which there was *strong disagreement* by a panel of 71 experts in the respiratory health effects of asbestos with the statement "pleural plaques alter lung function to a clinically significant degree."

5. In its DRAFT Quality Review Report, the EPA Scientific Advisory Board did not consider, or even mention, the findings of the *Public Health Assessment of the Libby Asbestos Site* that was prepared by the Division of Heath Assessment and Consultation of the United States Agency for Toxic Substances and Disease Registry (ATSDR), dated April 22, 2010. [5] In this report the ATSDR reports a very small 1.8% incidence of moderate to severe restriction in breathing capacity and does not include LPT (pleural plaques) among the strongest risk factors for restrictive changes in pulmonary function in *Libby Community Environmental Health Project* participants. The ATSDR position appears to be inconsistent with the EPA Scientific Advisory Board statement that "LPT is associated with reduced lung function."

RECOMMENDATIONS

1. The EPA Scientific Advisory Board should modify the statement that *"Pleural thickening is associated with restrictive lung function"* in Question 2 of its DRAFT Report to reflect the fact that this clearly pertains to *diffuse pleural thickening*, but does not necessarily pertain to localized pleural thickening [LPT]. The EPA Scientific Advisory Board should make it clear that, although *some* reports suggest a small, restrictive decrement in lung function associated with LPT, there are a number of other excellent reports that show no statistically or clinically significant decrement in lung function associated with asbestos-related LPT, especially after controlling for parenchymal changes indicative of interstitial fibrosis. The EPA Scientific Advisory Board should also make it clear that there is considerable scientific uncertainty about whether or not any significant

relationship between asbestos-related LPT and a decrement in lung function typically or universally exists at this time.

2. The EPA Scientific Advisory Board should delete the statement that "LPT is associated with reduced lung function" and replace it with a statement that takes into account the fact that a large body of scientific literature shows that there is no statistically or clinically significant decrement in lung function associated with asbestos-related LPT, especially after controlling for parenchymal changes indicative of interstitial fibrosis. Once again, the EPA Scientific Advisory Board should make it clear that there is considerable scientific uncertainty about whether or not any significant relationship between asbestos-related LPT and a decrement in lung function typically or universally exists at the present time.

3. Do not support the assertion that "LPT is associated with reduced lung function" as a reason for using localized pleural thickening [LPT] as the critical endpoint for deriving the inhalation reference concentration (RfC) in the IRIS assessment pertaining to Libby Amphibole Asbestos at this time. In view of numerous conflicting reports in the scientific and medical literature, as well as the considerable scientific uncertainty regarding whether or not any significant relationship between asbestos-related LPT and a decrement in lung function typically or universally exists, there is no clear-cut, scientifically rigorous basis for using the statement "LPT is associated with reduced lung function" as a reason for using LPT as the critical endpoint for deriving the RfC at the present time.

4. That the EPA Scientific Advisory Board convene an independent, objective panel of experts in asbestos-related respiratory health effects to develop scientifically rigorous *weight of evidence guidelines* for investigating any association between asbestos-related LPT and lung function. [24, 25, 26]

5. That the EPA Scientific Advisory Board subsequently convene an independent, objective panel of experts in asbestos-related respiratory health effects to perform a formal *weight of evidence evaluation* of the association between asbestos-related LPT and lung

function, based upon previously determined, scientifically *rigorous weight of evidence guidelines*, for the purpose of providing a clear-cut, robust, scientifically valid assessment of this association. [24, 25, 26]

6. Revisit the appropriateness of using the statement "LPT is associated with reduced lung function" as a reason for using localized pleural thickening [LPT] as the critical endpoint for deriving the inhalation reference concentration (RfC) in the IRIS assessment pertaining to Libby Amphibole Asbestos after the previously recommended *weight of evidence evaluation* has been completed.

7. Withhold publication of the final version of the final EPA Scientific Advisory Board Quality Review Report of the EPA DRAFT Assessment entitled Toxicological Review of Libby Amphibole Asbestos (August 2011) until after the previously recommended *weight of evidence evaluation* has been completed. The final version of this report should address the scientific appropriateness of using the statement "LPT is associated with reduced lung function" as a reason for using localized pleural thickening [LPT] as the critical endpoint for deriving the inhalation reference concentration (RfC) in the IRIS assessment pertaining to Libby Amphibole Asbestos based upon the *weight of evidence* contained in the recommended evaluation.

8. Consider, address and reference the *American College of Chest Physicians Consensus Statement on the Respiratory Health Effects of Asbestos* [4] with respect to any statements regarding the association of LPT and lung function in the final EPA Scientific Advisory Board Quality Review Report of the EPA DRAFT Assessment entitled Toxicological Review of Libby Amphibole Asbestos (August 2011).

9. Consider, address and reference the *Public Health Assessment of the Libby Asbestos Site* that was published by the Division of Heath Assessment and Consultation of the United States Agency for Toxic Substances and Disease Registry (ATSDR) [5] with respect to any statements regarding the association of LPT and lung function in the final EPA Scientific Advisory Board Quality Review Report of the EPA DRAFT Assessment entitled Toxicological Review of Libby Amphibole Asbestos (August 2011).

NOTES:

The professional opinions and commentary in this report are those of the report author and do not necessarily reflect the opinions of the Medical University of South Carolina or any other member of its faculty.

The report author has no personal, professional or financial conflicts of interest with respect to the literature reviews, assessments, professional opinions or professional commentary contained in this report.

The report author was retained by Exponent to objectively review the DRAFT Report of the EPA Scientific Advisory Board Quality Review of the EPA DRAFT Assessment entitled Toxicological Review of Libby Amphibole Asbestos (August 2011), dated August 30, 2012 and provide comments to the EPA and its Scientific Advisory Board. The author understands that the work was funded by W R Grace.

REFERENCES

1. Cugell DW, Kamp DW. Asbestos and the pleura. A review. Chest 2004; 125: 1103-1117.

2. Peacock C, Copley SJ, Hansell DM. Asbestos-related benign pleural disease. Clin Radiol 2000; 55:422-432.

3. British Thoracic Society. Pleural Plaques. Information for Health Care Professionals. London: 2011.

4. Banks DE, Shi R, McLarty J, et al. American College of Chest Physicians consensus statement on the respiratory health effects of asbestos: Results of a Delphi study. Chest 2009; 135: 1619-1627.

5. Agency for Toxic Substances and Disease Registry, Division of Health Assessment and Consultation. Public Health Assessment: Libby Asbestos Site, Libby County, Montana (EPA Facility ID MT0009083840). Atlanta: 2010.

6. Copely SJ, Wells AU, Rubens MB, et al. Functional consequences of pleural disease evaluated with chest radiography and CT. Radiology 2001; 220: 237-243.

7. Lilis R, Miller A, Godbold E, et al. Pulmonary function and pleural fibrosis: quantitative relationships with an integrative index of pleural abnormalities. Am J Ind Med 1991; 20: 145-161.

8. Paris C, Thierry S, Brochard P, et al. Pleural plaques and asbestos: dose-and- time response relationships based on HRCT data. Eur Respir J 2009; 34: 72-79.

9. Clin B, Paris C, Ameille J, et al. Do asbestosis-related pleural plaques on HRCT scans cause restrictive impairment in the absence of pulmonary fibrosis? Thorax 2011; 66: 985-991.

10. American Thoracic Society. Diagnosis and initial management of nonmalignant diseases related to asbestos. Am J Respir Crit Care Med 2004; 170: 691-715.

11. Ohlson CG, Rydman T, Sundell L, et al. Decreased lung function in long-term asbestos cement workers; a cross-sectional study. Am J Ind Med 1884; 5: 359-366.

12. Ohlson CG, Bodin L, Rydman T, Hogstedt C. Ventilatory decrements in former asbestos cement workers: a four year follow-up. Br J Ind Med 1985; 42: 612-616.

13. Jarvholm B, Sanden A. Pleural plaques and respiratory function. Am J Ind Med 1986; 10: 419-426.

14. Hjortsberg U, Orbaek P, Arborelius M, et al. Railroad workers with pleural plaques: I. spirometric and nitrogen washout investigation on smoking and nonsmoking asbestos-exposed workers. Am J Ind Med 1988; 14: 635-641.

15. Oliver LC, Eisen EA, Greene R, Sprince NL. Asbestos-related pleural plaques and lung function. Am J Ind Med 1988; 14: 649-656.

16. Bourbeau J, Ernst P, Chrome J, et al. The relationship between respiratory impairment and asbestos-related pleural abnormality in an active work force. Am Rev Respir Dis 1990; 142: 837-842.

17. Schwartz DA, Fuortes LJ, Galvin JR, et al. Asbestosis-induced pleural fibrosis and impaired lung function. Am Rev Respir Dis 1990; 141: 321-326.

18. Miller A, Lilis R, Godbold J, et al. Relationship of pulmonary function to radiographic interstitial fibrosis in 2,611 long-term asbestos insulators. Am Rev Respir Dis 1992; 145: 263-270.

19. Van Cleemput J, DeRaeve H, Verschakelen JA, et al. Surface of localized pleural plaques quantitated by computed tomogrraphy scanning – no relation with cumulative asbestos exposure and no effect on lung function. Am J Respir Crit Care Med 2001; 163: 705-710.

20. Miller A. Pleural plaques and lung function [Letter to the Editor]. Am J Respir Crit Care Med 2002; 165: 305-306.

21. Whitehouse AC. Asbestos-related pleural disease due to tremolite associated with progressive loss of lung function: serial observations in 123 miners, family members, and residents of Libby, Montana. Am J Ind Med 2004; 46: 219-225.

22. Sichletidis L, Chloros D, Chatzidimitriou N, et al. Diachronic study of pleural plaques in rural population with environmental exposure to asbestos. Am J Ind Med 2006; 49: 643-641.

23. Wilken D, Garrido MV, Manuwald U, Baur X. Lung function in asbestos-exposed workers, a systematic review and meta-analysis. J Occupat Med and Tox 2011; 6: 21.

24. Weed DL. Weight of evidence; a review of concept and methods. Risk Anal 2005; 25: 1545-1557.

25. Linkov I. Weight of evidence: what is the state of science? [Letter to the Editor]. Risk Anal 2006; 26: 573-575.

26. Linkov I, Loney D, Cormier S, et al. Weight-of-evidence evaluation in environmental assessment; review of qualitative and quantitative approaches. Sci Tot Environ 2009; 407: 5199-5205.

APPENDIX B – 5

Appendicies not included here

Comments to the SAB on the EPA document EPA/635/R-002A, "Draft Toxicological Review of Libby Amphibole Asbestos"

Suresh H. Moolgavkar, M.D., Ph.D.

Exponent, Inc.

Attachments

Appendix A: Moolgavkar Slides for presentation at the SAB meeting, Feb 6-8, 2012.

Appendix B: Moolgavkar October Report on the EPA document EPA/635/R-002A, "Draft Toxicological Review of Libby Amphibole Asbestos" together with slides shown at the listening session in October, 2011.

EXECUTIVE SUMMARY

This Executive Summary identifies my principal scientific concerns set forth more fully in the following report regarding the U.S. EPA's proposed quantitative risk assessment for cancer and non-cancer endpoints for Libby amphibole asbestos.

The EPA draft risk assessment for Libby amphibole ("2011 Draft") uses data on lung cancer and mesothelioma from a sub-cohort of the full cohort of Libby miners to estimate an Inhalation Unit Risk (IUR) for Libby amphibole. The 2011 Draft also uses data on localized pleural thickening from a sub-cohort of a cohort of workers at a vermiculite processing plant to estimate a Reference Concentration (RfC) for non-cancer adverse impacts on human health. While the current draft represents an enormous amount of effort, it has a number of significant scientific deficiencies.

1. Instead of using the full Libby cohort with follow-up through 2006, the 2011 Draft uses a greatly truncated sub-cohort of workers employed after 1959. This selection reduces the number of lung cancers from 111 in the full cohort to 32 in the sub-cohort and the number of mesotheliomas from 19 in the full cohort to 7 in the sub-cohort. The reduction in cohort size biases estimates of risk because older individuals are selectively eliminated from the sub-cohort.
2. The reduction in cohort size also leads to diminished power to detect departures from proportionality (effect modification by age) in the Cox model analyses of lung cancer and precludes the use of the Peto-Nicholson model for mesothelioma. The use of the Peto-Nicholson model is important because it recognizes the significant role of temporal factors, such as duration of exposure and time since exposure stopped, in determining mesothelioma risk following asbestos exposure.
3. For lung cancer, I recommend that a revised draft report analyze the entire Libby cohort and investigate carefully the effect modification of lung cancer risk by age. Since the lung cancer risk assessment is based on a life-table analysis, it is imperative to estimate age-specific relative risks.

4. For mesothelioma, I recommend that a revised draft report use the full cohort with 19 mesotheliomas and perform a full likelihood based time-to-tumor analysis using the Peto-Nicholson model as described in the body of my report, instead of the inadequately-justified Poisson regression that is used in this draft.
5. For the non-cancer risk assessment the 2011 Draft uses a small sub-cohort of workers employed at a vermiculite processing plant at Marysville, Ohio. While the full cohort investigated in Rohs et al. (2008) consists of 280 individuals with 80 cases of localized pleural thickening, the sub-cohort chosen in the 2011 Draft consists of 119 individuals with 12 cases of localized pleural thickening. Thus, the 2011 Draft discards without justification much of the available data.
6. The 2011 Draft does not provide adequate evidence to support the selection of localized pleural thickening as an adverse health impact for asbestos exposure. In previous Agency documents, no attempts have been made to derive an RfC for non-cancer adverse impacts on human health because the choice of an appropriate end-point was not clear. Therefore, the 2011 Draft sets a new precedent and it is imperative that a revised draft make clear why localized pleural thickening should be considered an adverse health impact rather than just a marker of asbestos exposure.
7. I recommend that a revised draft reevaluate the choice of localized pleural thickening as an adverse health impact and analyze the entire Rohs cohort data using appropriate statistical methods as described in the body of this report.
8. I recommend that a revised draft discuss the carcinogenic potency of Libby amphibole in context. Our understanding of the differential carcinogenic potencies of the different types of asbestos fibers has advanced considerably over the last decade. It is incumbent upon a revised draft to describe the contemporary literature on this topic and discuss the carcinogenic potency of Libby amphibole in relation to that of other asbestos fibers.

Background and Qualifications

I am a physician with a Ph.D. in Mathematics and post-doctoral training in Pharmacology, Biophysics, Epidemiology and Biostatistics. In April 2007, I became a Corporate Vice President and the Director of the Center for Epidemiology, Biostatistics and Computational Biology at Exponent, Inc., an international scientific consulting company. I retired from my position as a Full Member of the Fred Hutchinson Cancer Research Center in August 2008. I continue to be an Affiliate Investigator at the Center and Professor of Epidemiology and Adjunct Professor of Applied Mathematics at the University of Washington in Seattle. I am a cancer epidemiologist and research scientist. My main research interest is cancer epidemiology. I was instrumental in developing a biologically-based mathematical model, the two-stage clonal expansion (TSCE) model, often called the Moolgavkar-Venzon-Knudson (MVK) model, for the quantitative estimation and prediction of cancer risk. This model is recognized and used by cancer researchers worldwide.

I have served on the faculties of the Johns Hopkins University, Indiana University, the Fox Chase Cancer Center and the University of Pennsylvania. I have been a visiting scientist at the Radiation Effects Research Foundation in Hiroshima, the International Agency for Research on Cancer (IARC) in Lyon, and the German Cancer Research Center in Heidelberg.

I have served on numerous review panels and as a consultant to the National Cancer Institute (NCI); the Environmental Protection Agency (EPA); the California Air Resources Board; Health and Welfare, Canada; IARC; the CIIT Centers for Health Research; and the Health Effects Institute. I am the author or co-author of more than 160 papers in the areas of Epidemiology, Biostatistics, and Quantitative Risk Assessment, and have edited three books in these areas. Among these is a monograph, "Quantitative Estimation and Prediction of Human Cancer Risk," published by IARC, the agency that conducts cancer research under the auspices of the World Health Organization. I have served on the editorial board of *Genetic Epidemiology* and *Inhalation Toxicology* and am currently one of the editors of *Risk Analysis – An International Journal*. I am an elected member of the American

Epidemiological Society. I was given the Founders' Award by the CIIT Centers for Health Research in 1990 and the Distinguished Achievement Award by the Society for Risk Analysis in 2001. I am a Fellow of the Society for Risk Analysis, the pre-eminent international scientific society for risk assessment.

Among my publications are several papers on carcinogenesis following exposure to fibers. I was an Invited Expert at a workshop, "Mechanisms of Fiber Carcinogenesis," held at IARC in Lyon, France, in early November, 2005. I was the lead panelist for a symposium on fiber carcinogenesis held in Brussels in 2005.

Purpose of this Report

I have been retained by W.R. Grace to review and comment on the scientific issues in the draft risk assessment of Libby amphibole asbestos, which is a mixture of tremolite, winchite and richterite. The purpose of my review and comment is to assist the SAB and the EPA in ensuring that the final assessment of Libby amphibole is based on the best available science. I am intimately familiar with the Libby cohort data. I have analyzed these data with follow-up through 2002 (Moolgavkar et al., 2010) and many of my comments reflect the results of these analyses. I also had access to the Rohs database on a subset of which the 2011 Draft bases its estimate of the RfC for Libby amphibole. I have analyzed these data as well, but have not published the results.

I had previously made oral comments on the 2011 Draft at a "listening session" organized by the EPA in October, 2011. At that time, I also provided written comments to address more fully the technical details that could not be covered in a short verbal presentation. I attach my previous written comments to this document as appendix B. The slides of my October presentation at the listening session are appended to those written comments.

In these comments to the SAB, I summarize the main scientific issues raised by the 2011 Draft risk assessment. I do not discuss the specific toxicity values derived in the 2011 Draft because such numbers can be meaningfully discussed only after the scientific issues have been properly addressed.

The main goals of the 2011 Draft risk assessment are to develop an inhalation unit risk (IUR) for cancer (lung cancer and mesothelioma) and a reference concentration (RfC) for non-cancer endpoints associated with exposure to Libby amphibole.

Cancer Risk Assessment

The current IRIS Inhalation Unit Risk (IUR) for asbestos-associated cancer is based on combining separate slope factors for lung cancer and mesothelioma using a life-table analysis. The general framework for developing an IUR in the 2011 Draft is similar to that used by the Agency for the development of an asbestos cancer slope factor for the IRIS database in 1993, which was based on the risks estimated in an earlier Agency report by Nicholson (1986). The models and methods used in the 2011 Draft to derive individual slope factors for lung cancer and mesothelioma are different, however.

In the 2011 Draft, the EPA develops an IUR for cancer in the following three steps. The procedure is similar, but not identical, to the procedure used in the 1993 IRIS document.

1. Estimate potency for lung cancer (K_L) from the occupational cohort data using a relative risk (RR) model. The RR is assumed to be a function of cumulative exposure. Whereas the 1986 Nicholson analysis was based on regressions through standardized mortality ratios (SMRs), the current 2011 Draft document uses the Cox proportional hazards model applied to a (truncated) Libby worker cohort.

2. Estimate potency for mesothelioma from the occupational cohort data using an absolute risk model. The 1986 analysis was based on a model originally developed by Peto et al. (1982) and then adopted by Nicholson, and which I call the Peto-Nicholson model. In this model, which is based on ideas of multistage carcinogenesis, the hazard function for mesothelioma is a function of exposure concentration, duration of exposure, and time since exposure stopped. The model is

linear in exposure concentration, but non-linear in the time variables. Therefore, this model recognizes explicitly the role of pattern of exposure in determining risk. In this model, risk cannot be expressed as a function of cumulative exposure. The 2011 Draft bases its estimate of potency instead on a Poisson regression analysis of mesothelioma deaths in the same truncated data set used for the lung cancer potency estimate, using cumulative exposure as the measure of exposure. In a giant step backwards, the 2011 Draft does not recognize the important role of the time variables in determining risk.

3. In the final step, risk estimates for mesothelioma and lung cancer are combined using a life-table analysis for lung cancer to arrive at the IUR for cancer.

For its current analyses of lung cancer and mesothelioma, the 2011 Draft uses the sub-cohort of workers employed after 1959 and followed up through 2006. The Draft give two reasons for the choice of this dataset rather than the full Libby cohort. First, it argues that exposure is better characterized[1] in this sub-cohort and second, proportionality of hazards for lung cancer holds in this sub-cohort, and therefore the issue of effect modification by age does not have to be addressed. There is some merit to the first reason, but the second reason does not stand up to scrutiny. In fact, as explained below, effect modification by age is an important feature of many epidemiologic cohort data sets that span several decades and should, in fact, be explicitly addressed in any risk assessments, particularly ones that rely on life table analyses as does the Agency assessment for lung cancer.

[1] The 2011 Draft repeats the old canard (page 5-78 of the report) about non-differential covariate measurement errors leading to risk estimates biased towards the null. This statement, although widely repeated by epidemiologists, is incorrect. First, not only must the misclassification be non-differential, it must satisfy other conditions (e.g., Jurek et al., 2005) for the result to hold. Second, the statement applies to the expectation of the risk estimate, not to the value of the estimate from any single study. Thus, it is possible to have non-differential misclassification that satisfies all the required conditions but the result of a single study may actually overestimate the risk. As Jurek et al. (2005) state, "...exposure misclassification can spuriously increase the observed strength of an association even when the misclassification process is non-differential and the bias it produced is towards the null." Similar discussion is provided by Thomas (1995) and Weinberg et al. (1995).

Lung Cancer

The Libby workers' cohort is the logical choice of dataset on which to base risk estimates for lung cancer and mesothelioma. Over the years there have been numerous publications based on analyses of this cohort (Amandus et al., 1987; McDonald et al., 1986, 2002, 2004; Sullivan, 2007; Moolgavkar et al., 2010; Larson et al., 2010). As the most contemporaneous studies with the longest follow-up, the studies by Sullivan, Moolgavkar, and Larson are the most relevant to this risk assessment. Both Moolgavkar et al. (2010) and Larson et al. (2010) used the Cox proportional hazards model, as does the 2011 Draft, and arrived at similar estimates of RR (~1.1 for 100f/cc-y cumulative exposure). I note here that this RR is quite a bit smaller than that estimated in other asbestos occupational cohorts. The RR associated with exposure to asbestos in the South Carolina Textile Workers' cohort, for example, is substantially larger[2] (Hein et al., 2007; Richardson, 2009).

The estimation of a single RR for all ages should be interpreted as an averaging of risks over all ages and is appropriate only as a summary measure of risk in the entire cohort. However, a life-table analysis as conducted by the Agency in the 2011 Draft and previous risk assessments, involves the use of age-specific lung cancer mortality rates from a standard population multiplied by the RR to estimate the number of excess lung cancer deaths as a consequence of exposure to asbestos. Therefore, when a life-table analysis is performed, it becomes important to investigate RR as a function of age, i.e., to investigate effect modification by age. The 2011 Draft had a great opportunity here to investigate effect modification by age but appears to have gone to great lengths not to do so. In fact, the 2011 Draft chose a sub-cohort for analyses in which effect-modification by age had been eliminated. As a result, the Draft fails to evaluate the critical importance of effect modification thus biasing the IUR for lung cancer.

There are compelling reasons to use the entire Libby cohort rather than the sub-cohort that the Agency chooses to use.

[2] Hein et al. (2007) report an RR of about 3 associated with 100 f/cc-yr cumulative exposure as compared to an RR of about 1.11 in Libby for the same cumulative exposure.

1. By discarding more than two-thirds of the lung cancers (111 in the full cohort followed up until 2006 (Larson et al., 2010) as opposed to 32 in the sub-cohort used by the Agency), the power to detect effect-modification by age is greatly diminished. Effect modification by age is an important feature of many epidemiologic data sets (Moolgavkar, 2012), as discussed in more detail in my comments at the October listening session (see Appendix B of this report) and age-specific relative risks should be applied in a life-table analysis. In particular, there is strong evidence of effect modification of lung cancer risk by age in the Libby cohort as can be seen in figure 1 below. The 2011 Draft recognizes that effect modification by age is important in the entire cohort (page 5-76), but then effectively ignores it by choosing a sub-cohort in which it is no longer statistically significant. The single estimate of RR used in the 2011 Draft under-estimates risk at the younger ages and over-estimates it at the older ages (see figure 1 below).

2. The sub-cohort consists of workers who entered the work force after 1959. With follow-up until 2006, there are probably few sub-cohort members over the age of 65 by the end of the study, the age at which the incidence of lung cancer begins to increase rapidly. Therefore, the Agency potency estimates for lung cancer are based primarily on individuals below the age of 65. In particular, with the life-table analysis going out to age 85, it is important that lung cancer at the older ages make some contribution to the estimate of RR. As stated above age-specific RRs should be used in the life-table analyses. If the Agency insists on using a single estimate of RR, it should clearly be estimated from a dataset that spans the entire range of ages. At the very least, a comprehensive uncertainty analysis should be undertaken to investigate how the choice of sub-cohort and the assumption of no effect modification affects the IUR for lung cancer.

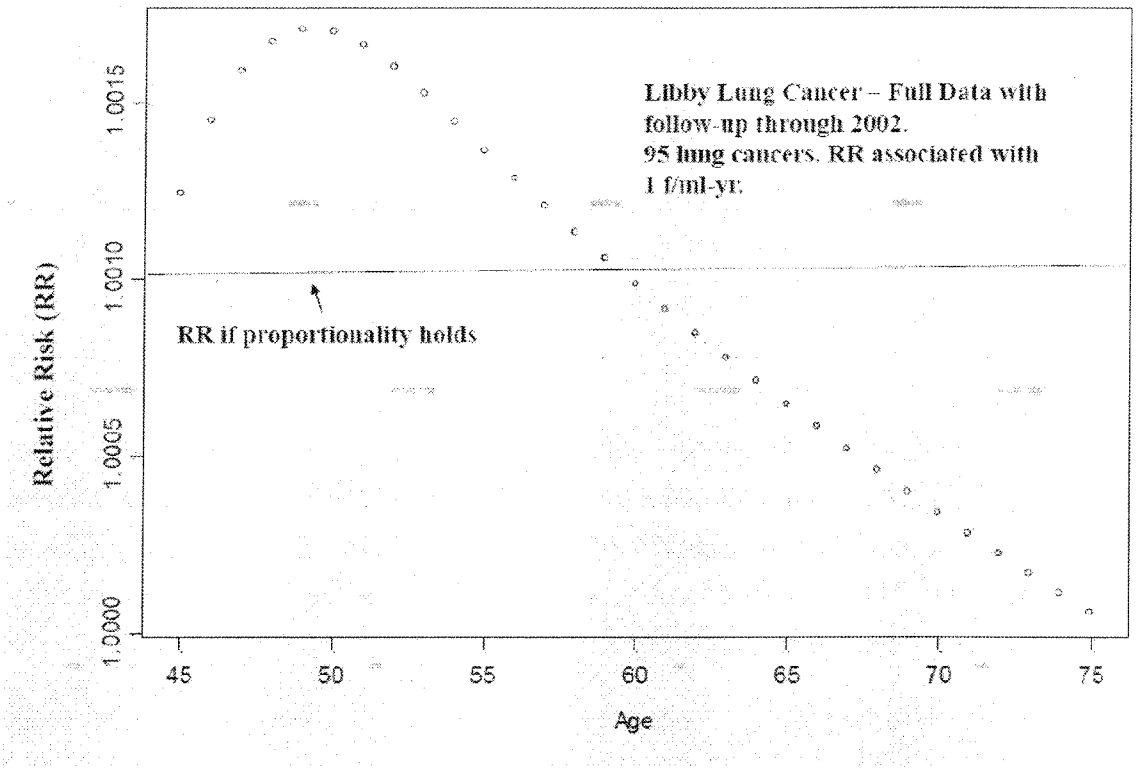

Figure 1. Analysis of lung cancer in the full Libby cohort followed up through 2002 (Sullivan, 2007; Moolgavkar et al., 2010) using natural splines to model RR as a function of age. RR on the y-axis is associated with a cumulative exposure of 1f/cc-yr. Note the strong effect modification by age, which can also be seen in figure 2 below and in slides 8 and 9 in my presentation at the listening session. These slides are appended to my October written comments (Appendix B). A test for effect modification by age is statistically significant. More details are in my October report (Appendix B).

Figure 2 below is taken from a publication by Richardson (2009) analyzing the lung cancer risk associated with asbestos exposure in that cohort. The figure shows the strong effect modification by age in this cohort. Richardson uses the biologically-based two-stage clonal expansion (TSCE) model also known as the Moolgavkar-Venzon-Knudson (MVK) model and shows not only strong effect modification by age, but also that cumulative exposure to asbestos is a poor measure of exposure

for lung cancer risk assessment. In fact, as is the case of mesothelioma, temporal pattern of exposure is important in determining risk. We have conducted similar analyses for lung cancer in the Libby cohort using the TSCE model and can confirm Richardson's findings in the South Carolina cohort, although the magnitude of the lung cancer risk associated with exposure to Libby amphibole asbestos is much smaller.

Cancer Causes Control (2009) 20:917–923

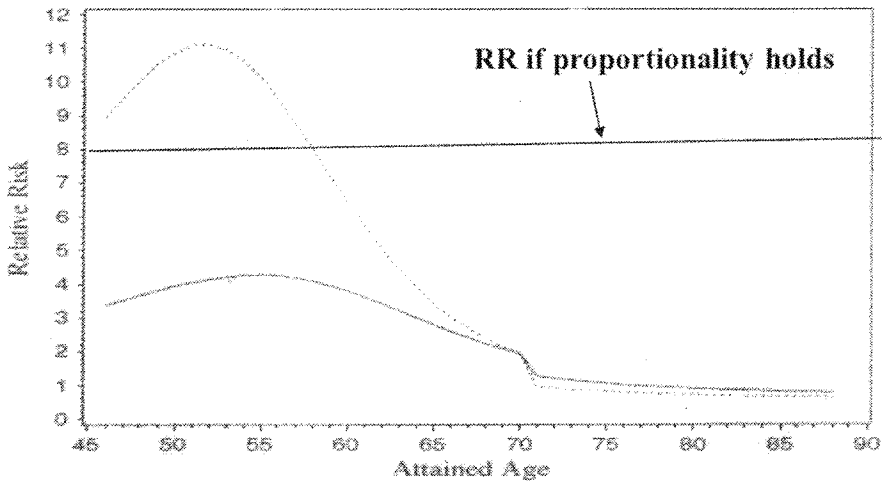

Fig. 2 Lung cancer relative risk by attained age. Predicted impact of asbestos exposure at intensities of 5 (dashed line) and 2.5 fiber/ml (solid line) based upon fitting of the two-stage clonal expansion model (predicted relative risks based on the model parameters shown in Table 2 and allowing for asbestos exposure effect as shown in Table 3, Model 2). Exposure commences at age 20 years and terminates at age 60 years. Ten-year lag assumption

Thus, there is strong evidence that 1) effect modification by age is an important feature of asbestos-associated lung cancer risk, and 2) lung cancer risk after asbestos exposure is a function of the entire exposure history, not just cumulative exposure. In my oral and written comments for the October listening session, I provided other examples showing that effect modification by age, i.e. non-proportionality of hazards is ubiquitous in epidemiologic data sets that span a wide range of ages. Please see the Appendix B for details.

<u>Recommendations for lung cancer risk assessment</u>

1. Utilize the entire Libby data set of Larson et al. (2010) for risk assessment using the proportional hazards model.
2. Use flexible statistical methods, such as spline smoothers, to explore carefully effect modification by age in the data.
3. Explore the role of patterns of exposure in determining risk by using biologically-based models, such as the multistage model and the TSCE (MVK) model.
4. Explore approaches other than the life-table approach for estimating IUR. For example, robust estimation of excess risk may be directly possible from analyses using approaches based on ideas of multistage carcinogenesis, such as the TSCE model.
5. If a life-table approach is necessary, use age-dependent RRs to account for effect modification by age.

Mesothelioma

Analyses of mesothelioma in the Agency report is based on the same sub-cohort as the lung cancer analyses. Whereas there are 19 mesotheliomas in the full cohort, there are only 7 in the sub-cohort used by the Agency. The risk estimate obtained by analysis of these 7 cases is adjusted upward to address under-ascertainment of mesothelioma cases using a method proposed by Kopylev (2011). As discussed below, this adjustment is poorly justified and ill-advised.

It is well known from the work of Peto and Nicholson that temporal factors, such as duration of asbestos exposure and time since exposure stopped, play an important role in determining mesothelioma risk from exposure to asbestos. The 2011 Draft has chosen to ignore this fundamental fact in abandoning the Peto-Nicholson model, which was used in its 1986 risk assessment and which has been shown to describe the data well in multiple occupational cohorts (Berman & Crump, 2008), in favor of a poorly-justified Poisson regression model.

The Peto-Nicholson hazard function for mesothelioma mortality is of the form $h(t) = K_M * g(t)$, where $g(t)$ is a power of time since exposure started and depends also on fiber concentration, and K_M is a constant that depends on fiber type. I

recommend that a revised draft use a generalization (Berman & Crump, 2008) of the original formula to accommodate time-varying exposure concentrations:

$$g(t) = 3 \int_0^{t-10} E(u)(t-u-10)^2 du,$$

where *g(t)* is the mortality rate (per year) at year t after start of exposure and *E(u)* at time *u* is the concentration of asbestos fiber expressed as fibers/ml.

The 2011 Draft states that the Peto-Nicholson model was tried, but did not describe the data as well as the Poisson model that it ultimately used. It is not at all clear, however, that the Peto-Nicholson model was tested appropriately. The version of the model used by Berman and Crump (2008), which accommodates time-varying exposure concentrations, should have been used and a full likelihood time-to-tumor analyses performed to estimate not only K_M, but also the exponent of the duration of exposure. With only 7 cases, such an analysis is probably not feasible. In my opinion, the full Larson data set should be analyzed using the Peto-Nicholson model. With the Poisson regression adopted in the 2011 Draft, all information about time-to-tumor is lost. It is also not clear from the description provided in the report how the Poisson regression was performed. For example, the report should state clearly what contribution each individual in the cohort made to the expectation of the Poisson model. Even if Poisson regression is used for these analyses, it is not clear why it is necessary to use Bayesian MCMC methods. Likelihood-based analyses using generalized linear models appear to be straightforward. The numerous analyses performed and reported on this small dataset are unjustified. How can one discriminate among the many models used with only 7 cases of mesothelioma in the dataset? Small differences in the deviance information criterion (DIC), or whatever criterion is used to measure relative fits, are hardly informative with this small dataset.

Finally, the Agency used a method proposed by Kopylev (2011) to adjust risk upward by a factor 1.39 to compensate for under-ascertainment of mesothelioma deaths in the sub-cohort. I believe this adjustment is ill-advised for the following reasons. First, the under-ascertainment of total asbestos exposure because of

exposure to asbestos from other sources should be considered before any adjustment is made for under-ascertainment of mesothelioma (or any other) deaths. Many of the workers at the Libby mines worked there only for short periods of time. A substantial number in the full Libby cohort was employed there for less than one year. It is clear from the data in Peipins et el. (2003) that residents of Libby were employed in other jobs that could have exposed them to asbestos. It is therefore highly likely that exposure to asbestos is under-estimated in the cohort, particularly among short-term workers. This is not a problem peculiar to Libby. It is ubiquitous with occupational cohort studies and the only way to get around it is to perform a case-control study nested within the cohort. Second, I do not believe that the data on under-ascertainment used for estimating the adjustment factor is reliable because standards for the reporting of mesothelioma as a cause death varied from place to place. Third, the adjustment factor is based on a Poisson regression analysis and it is not clear that the same Poisson models were used in the report and in Kopylev et al. (2011). The adjustment factor using a proper likelihood based analysis using the Peto-Nicholson model would likely be different. Fourth, the adjustment factor applied in the Agency report is the one derived by Kopylev et al. (2011) based on the full dataset. It is not clear that the same adjustment factor would be obtained if the method were applied directly to the sub-cohort. Finally, with the amount of scrutiny received by the Libby population it is hardly likely that under-ascertainment is a problem. A revised draft should not apply any adjustment factor for under-ascertainment.

Recommendations for mesothelioma risk assessment

1. Use the entire Libby data (follow-up through 2006) used by Larson et al. (2010) with 19 cases of mesothelioma.
2. Use a likelihood-based time-to-tumor analysis with the Peto-Nicholson model and attempt to estimate both K_M and the exponent in the hazard function so that the dependence of risk on pattern of exposure is explicitly recognized. Moolgavkar et al. (2010) estimated $K_M = 0.5$, half the estimate used in the 1986 EPA asbestos risk assessment. Moolgavkar et al. (2010) could not estimate the exponent because they had information only on the

number (15) of mesothelioma deaths in the cohort followed through 2002, but not on which specific individuals died of the disease. With this information, only K_M can be estimated. Another option would be to use the TSCE model. Both the Peto-Nicholson and the TSCE model recognize and explicitly incorporate pattern of exposure in the hazard function.

3. Abandon the attempt to adjust for under-ascertainment of mesothelioma deaths for reasons set forth above.
4. Abandon the attempt to estimate half-life of Libby asbestos in the pleura. The simple formulation used has no biological interpretation as discussed in my report for the October listening session (Appendix B).

Non-Cancer Risk Assessment

The previous Agency IRIS document for asbestos provides no estimate of an RfC for non-cancer endpoints because of the absence of suitable data for. Thus, the 2011 Draft sets a new precedent in estimating an RfC for non-cancer endpoints. It is therefore of critical importance that the health endpoint on which the RfC is based be carefully evaluated, the appropriate datasets for analyses be identified, and the proper statistical methods be used. The 2011 Draft bases its risk assessment for non-cancer endpoints on a cohort of workers involved in the processing of vermiculite at a plant in Marysville, Ohio, and analyzed by Lockey et al. (1984) and Rohs et al. (2008). The Agency risk assessment is based on a sub-cohort of the cohort analyzed by Rohs et al. (2008). The end-point of interest for the analyses is localized pleural thickening. The Rohs et al. cohort consists of 280 individuals with 80 cases of pleural thickening. The sub-cohort chosen by the Agency includes 119 participants with 12 cases of pleural thickening. Therefore, as is the case for lung cancer and mesothelioma, the 2011 Draft discards much of the data for the analyses in this report.

A fundamental question that is not adequately addressed in the 2011 Draft is whether localized pleural thickening is an adverse health impact or simply a marker of asbestos exposure. While the 2011 Draft cites literature to suggest that localized pleural thickening is associated with various clinical endpoints, such as chest pain, it provides no evidence that these associations are causal. For

example, urinary cotinine, because it is a marker of cigarette smoking, is undoubtedly associated with lung cancer but it clearly does not cause lung cancer.

The 2011 Draft says, "...more accurate exposure data are considered to be those from 1972 and later, as these data were based on analytical measurements." Based on these considerations, the Agency chose from the Rohs cohort the sub-cohort consisting of workers who began work in 1972 or later. The radiographic examination of these workers was conducted over the period 2002-2005. However, in their paper, Rohs et al. identified 1973, not 1971, as the year after which "...more comprehensive environmental exposures were available..."The sub-cohort of workers hired after 1973 consists of 94 individuals with 10 cases of pleural abnormalities. I had access to the original Rohs database[3] and it includes an identifier for workers hired after 1973 but not for those hired after 1971. The report does not explain this discrepancy.

I have analyzed the full Rohs dataset using logistic regression and spline smoothers to explore exposure-response relationships. The results are shown in figure 3 below. This figure shows that most of the exposure data (the thickness of the rug at the bottom of the figure reflects the number of data points) lies in the range of 0-3 f/cc-yr. In this range of exposure, the flexible exposure-response model does not support a monotonic increasing exposure-response relationship. While the exposure-response relationship is consistent with linearity above 3 f/cc-yr, it is statistically insignificant in this range, possibly because of the paucity of data. There also is evidence of confounding by age (see figure 3).

One of the important criteria enunciated by the Agency for study selection for non-cancer risk assessment is that the exposure-response relationship be robust to adjustment for potential confounders. Thus, on page 5-11, the report states, "Amandus et al. (1987b) report that although cumulative exposure and age are both significant predictors of small opacities, cumulative exposure was not significantly related to pleural abnormalities when age is included in the model, thus limiting the usefulness of these data for RfC derivation based on pleural

[3] As the 2011 Draft describes in appendix F, the exposure estimates in the original Rohs database have been revised for the current risk assessment. I do not have access to the revised estimates of exposure.

abnormalities." In listing the advantages of the Rohs sub-cohort the Agency used, the report on page 5-14 (number 6) clearly states that it considers the absence of any evidence of confounding in this dataset a distinct advantage. I do not have access to the exact data used by the Agency, but I have analyzed full Rohs dataset as described above and there is strong evidence of confounding by age. By its own criteria, the Agency should not be using this dataset for derivation of an RfC.

Finally, the 2011 Draft uses various lags in the analyses of the sub-cohort. The use of lags for the analyses of pleural abnormalities makes no sense. Lags can be used in analyses of hazard or incidence functions when the diagnosis of an end-point, such as cancer, is made at a well-defined point in time. It is unscientific to use lags in the analyses of prevalent conditions, which could have occurred many years before the condition was noted. In the Rohs database all radiography was performed between 2002 and 2005, when pleural abnormalities were noted. These could have occurred many years before the radiography was done. What is the interpretation of a lag in this situation?

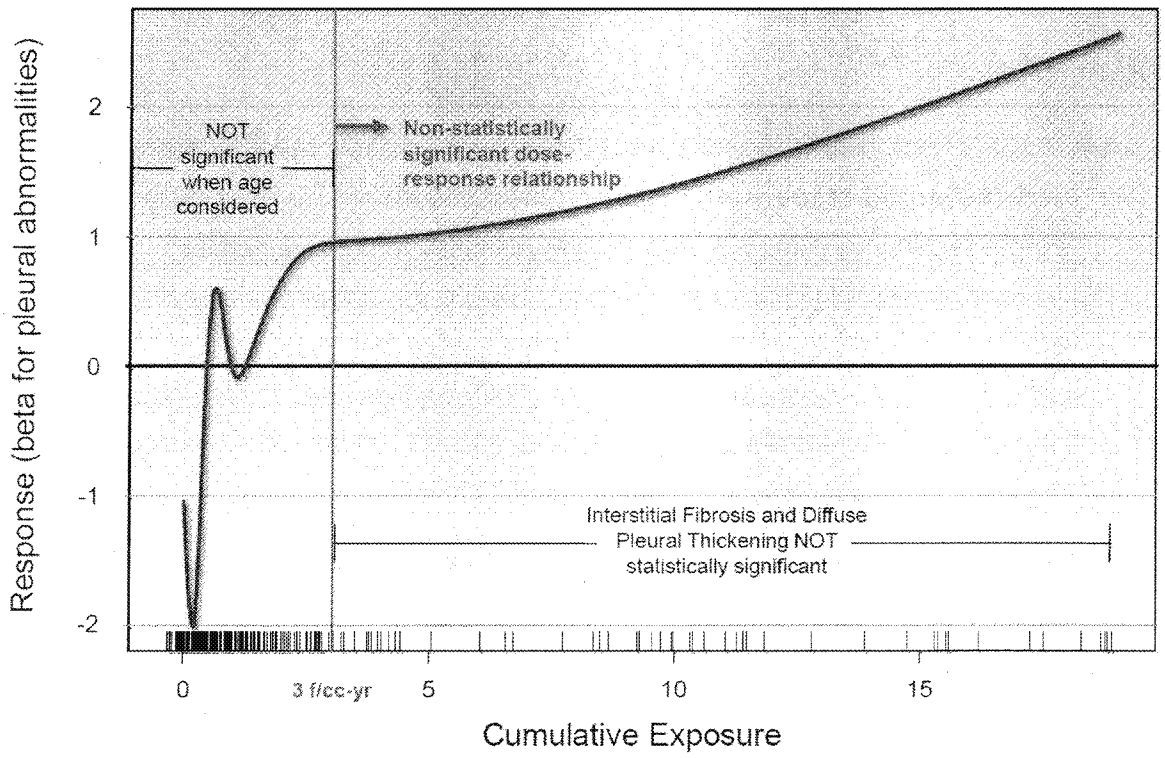

Figure 3 Exposure-response for localized pleural thickening as a function of cumulative exposure in the Rohs dataset.

Recommendations for Non-Cancer Risk Assessment

1. If localized pleural thickening is retained as the endpoint of interest, the full dataset should be used.
2. However, the Agency should acknowledge that the Rohs data does not satisfy its own criteria for use as a dataset for derivation of an RfC.
3. Although I am not a pulmonologist, I am concerned about calling localized pleural thickening an adverse event of clinical significance. The 2011 Draft does not provide adequate evidence to support this position.
4. Fat in the pleura is often mistaken for localized thickening on plain X-ray. Therefore, there may be considerable misclassification of the end-point in the data.
5. The Agency should recognize, as it did in the 1986 risk assessment, that there may not be an appropriate dataset for the derivation of an RfC for non-cancer end-points.

Other Issues

1. There is little doubt that mortality from lung cancer, mesothelioma and non-malignant respiratory disease (NMRD) was increased among workers employed at the mines in Libby. The real issue here is whether environmental exposure to Libby amphibole asbestos increased the risk of mortality from asbestos-associated diseases in the population of Libby. To address this question, the Agency for Toxic Substances and Disease Registry (ATSDR) conducted a mortality study in Libby in 2000. The Agency report should discuss this study in more detail.

   The ATSDR undertook a study of mortality from specific causes in the Libby area over the 20-year period 1978-1998. Numbers of deaths from specific causes were compared with numbers that would be expected under national and Montana death rates. Standard epidemiological and statistical techniques were used to compute SMRs and their confidence intervals.

Given the asbestos exposure in this population the main cancers of interest were lung cancer and mesothelioma. Mortality over the period of this study would be expected to reflect the impact of environmental exposure to high levels of Libby amphibole.

The ATSDR reports a small non-significant increase in lung cancer deaths within Libby City and the extended Libby area using Montana death rates as the standard. With US death rates as the standard, no increase in lung cancer deaths is reported. Thus, the number of lung cancer deaths over the period of the study offers no evidence that environmental exposures contributed to the lung cancer mortality over the period 1978-1998.

The ATSDR reports four cases of mesothelioma over the period of the study. Since the background rate of mesothelioma is close to zero, this number points to a significant elevation of risk in the Libby area. However, four cases of mesothelioma are identified in the McDonald (2002, 2004) occupational cohort, and it seems highly likely that these are the cases identified by ATSDR. Thus, the cases in the ATSDR study can, in all likelihood, be explained on the basis of occupational exposure. As in the case of lung cancer, this study offers no evidence that environmental exposure contributed to mesothelioma deaths in the Libby area.

Among the causes of death other than cancer, of most interest are the non-malignant respiratory diseases (NMRD), particularly asbestosis. Eleven deaths from pneumoconioses are reported over the period of the study. All of these are labeled asbestosis in the ATSDR report, although it is not clear how this diagnosis was verified. In any case, the SMR is reported to range between 36 and 47 (depending on the geographic area of analysis) using the Montana rates as the standard, and between 60 and 75 using the US rates as the standard. It is clear that deaths from asbestosis were significantly elevated. Of note, however, is the fact that 10 of the 11 deaths were among males suggesting strongly that occupational exposures were involved in these deaths. There is little evidence that environmental

exposures were involved in the deaths from asbestosis, which is known to be associated with high levels of exposure to asbestos.

In conclusion, there is little evidence that environmental exposure to asbestos contributed to the deaths from respiratory cancer, mesothelioma and asbestosis in the Libby area over the period 1978-1998.

2. A serious deficiency of the 2011 Draft is that it fails to provide context for the carcinogenicity of Libby amphibole. In the last decade, our understanding of the differential carcinogenic potencies of the different types of asbestos fibers has advanced considerably (Hodgson & Darnton, 2000; Berman & Crump, 2008). It is important that the Agency put the carcinogenicity of Libby amphibole in perspective by discussing where in the range of potencies of the various asbestos fibers, the potency of Libby amphibole lies. The paper by Hodgson & Darnton (2000) is not even referenced in this Agency draft and the paper by Berman & Crump (2008) is only mentioned in passing.

References

Amandus HE and Wheeler R. The morbidity and mortality of vermiculite miners and millers exposed to tremolite-actinolite: Part II. Mortality. Am J Ind Med. 1987:11:15-26.

ATSDR (Agency for Toxic Substances and Disease Registry). Health Consultation: Mortality from asbestos in Libby, Montana. 12-12-2000.

Berman DW, Crump KS. Update of potency factors for asbestos-related lung cancer and mesothelioma. Crit Rev Toxicol 2008;38 Suppl 1:1-47.

Environmental Protection Agency. 1993. Integrated Risk Information System, Asbestos.

Hein MJ, Stayner LT, Lehman E, Dement JM. Follow-up study of chrysotile textile workers: cohort mortality and exposure-response. Occup Environ Med 2007;64(9):616-25.

Hodgson JT, Darnton A. 2000. The quantitative risks of mesothelioma and lung cancer in relation to asbestos exposure. Ann Occup Hyg **44: 565-601.**

Jurek AM, Greenland S, Maldonado G, Church TR. Proper interpretation of non-differential misclassification effects: expectations vs observations. Int J Epidemiol 2005;34(3):680-7.

Kopylev L, Sullivan PA, Vinikoor LC, Bateson TF. Monte Carlo analysis of impact of underascertainment of mesothelioma cases on underestimation of risk. Open Epidemiology Journal 2011;4:45-53.

Larson TC, Antao VC, Bove FJ. Vermiculite worker mortality: estimated effects of occupational exposure to Libby amphibole. J Occup Environ Med 2010;52(5):555-60.

McDonald JC, McDonald AD, Armstrong B, and Sebastian P. 1986. Cohort study of mortality of vermiculite miners exposed to tremolite. Br J Ind Med. 1986: 43: 436-444.

McDonald JC, Harris J and Armstrong B. Cohort mortality study of vermiculite miners exposed to fibrous tremolite: an update. Ann Occup Hyg. 2002; 46, Supp 1: 93-94.

McDonald JC, Harris J and Armstrong B. Mortality in a cohort of vermiculite miners exposed to fibrous amphibole in Libby, Montana. Occup Environ Med., 2004, 61:363-366.

Moolgavkar SH. Multistage carcinogenesis and epidemiologic studies of cancer in "Modeling and Inference in Biomedical Science - In Memory of Andrei Yakovlev". edited by Almudevar, A.L., Hall, W.J. and Oakes, D. Institute of Mathematical Statistics Collections Series, to appear, 2012.

Moolgavkar SH, Turim J, Alexander DD, Lau EC, Cushing CA. Potency factors for risk assessment at Libby, Montana. Risk Anal 2010;30(8):1240-8.

Nicholson WJ. Airborne asbestos health assessment update.: US Environmental Protection Agency (USEPA), Office of Health and Environmental Assessment; 1986.

Peipins LA, Lewin M, Campolucci S, Lybarger JA, Miller A, Middleton D, et al. Radiographic abnormalities and exposure to asbestos-contaminated vermiculite in the community of Libby, Montana, USA. Environ Health Perspect 2003;111(14):1753-9.

Peto J, Seidman H, Selikoff IJ. Mesothelioma mortality in asbestos workers: implications for models of carcinogenesis and risk assessment. Br J Cancer 1982;45(1):124-35.

Richardson DB. Lung cancer in chrysotile asbestos workers: analyses based on the two-stage clonal expansion model. Cancer Causes Control 2009;20(6):917-23.

Rohs AM, Lockey JE, Dunning KK, Shukla R, Fan H, Hilbert T, et al. Low-level fiber-induced radiographic changes caused by Libby vermiculite: a 25-year follow-up study. Am J Respir Crit Care Med 2008;177(6):630-7.

Sullivan PA. Vermiculite, respiratory disease, and asbestos exposure in Libby, Montana: update of a cohort mortality study. Environ Health Perspect 2007;115(4):579-85.

Thomas DC. Re: "When will nondifferential misclassification of an exposure preserve the direction of a trend?". Am J Epidemiol 1995;142(7):782-4.

Weinberg CR, Unback DM, Greenland S. Weinberg et al. reply [Letter]. Am J Epidemiol 1995;142:784.

APPENDIX B – 6

COMMENTS ON THE EPA DRAFT RISK ASSESSMENT FOR LIBBY AMPHIBOLE

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As a member of the interested public and a consultant to W. R. Grace, I was given a limited amount of time to testify before the SAB in February, 2012. During that meeting, members of the SAB requested that the Agency provide more support for its risk assessments asking for substantive sensitivity analyses of both the IUR for the cancer endpoints and the RfC for the non-cancer endpoint. Members of the SAB also suggested that numerous additional papers be reviewed and requested access to some datasets. Members of the SAB have now posted updated comments, and the EPA has made a limited dataset available to the general public. My comments here are in response to the posted comments by the SAB, and are based, in part, on reviews of the additional papers that the SAB thought should be considered and on analyses of the limited dataset on pleural plaques made available to the public.

A. Reference Concentration (RfC) for non-cancer adverse effects using discrete pleural thickening (pleural plaques) as the relevant endpoint.

Two fundamental issues arise. Are pleural plaques simply a marker of asbestos exposure, or do they represent an adverse clinical condition? Second, if plaques do represent an adverse clinical condition, are the data and methods used by the Agency valid? I address the second question first.

The data used by the Agency for the derivation of an RfC are inappropriate.

This opinion is based on the following facts.

- The RfC is based on a small subcohort of the cohort of vermiculite workers analyzed by Rohs et al. (2008). The Rohs dataset reports 68 pleural plaques among 280 individuals. The Agency subcohort consists of 118 individuals with 12 cases of pleural plaques. The power to detect any confounding in this small dataset is greatly diminished. It is inappropriate to base a risk assessment on such a small dataset, particularly when the Agency is setting a precedent by proposing for the first time an RfC for non-cancer endpoints for asbestos exposure.
- My previous analysis of the full Rohs dataset indicates **strong confounding by age with the parameter estimate for exposure to Libby amphibole becoming greatly attenuated in joint analyses with age**. When both age and BMI are included in the analysis, the coefficient for Libby amphibole becomes borderline insignificant.
- By the Agency's own criteria when rejecting the Amandus study as a basis for the RfC, the Rohs dataset cannot be used for the estimation of an RfC. Selecting a small subcohort to get around the issue of confounding by age and BMI is not the appropriate way to address this issue.
- **Conclusion**: The Rohs dataset and subsets of it are not suitable for the derivation of an RfC.

The model used by the Agency for the derivation of an RfC is inappropriate.

Even if the data chosen by the Agency for developing an RfC were appropriate, the model used is not. This opinion is based on the following facts.

- Despite a choice of a large number of exposure-response models available in the standard benchmark dose software (BMDS) developed and distributed by the Agency, in this risk assessment, the Agency chose to use a model, the Michaelis-Menten model, which is not among

the models in the BMDS. The Michaelis-Menten model is widely used for enzyme kinetics and receptor binding and its properties make it unsuitable for a dose-response analysis for the estimation of an RfC. The model requires the estimation of a plateau, which is biologically unrealistic. Even in the dose-response modeling for cancer, a relatively rare condition even with high exposures, models with a plateau, implying that a certain fraction of the population is immune, are not used.

- The Agency forced the model through a background prevalence for pleural plaques of 1%, even though the model allows the estimation of a background. There is little support in the literature for any specific background prevalence of pleural plaques. Fixing the background at 1% probably increased the slope of the exposure-response relationship at low exposures. The Agency probably chose to fix the background prevalence because the small data set does not permit the estimation of the background, slope and plateau simultaneously. **As it is both estimated parameters were statistically insignificant (table 4 of the supplemental material provided by the Agency), thus suggesting that the data are consistent with no impact of exposure to Libby amphibole on pleural plaques in these data. Ironically, however, statistical insignificance of the parameters implies a wider confidence interval and consequently a lower estimate of the BMCL[1]. The greater the uncertainty, the lower the BMCL.**
- Many of the models tried by the Agency fit the data (by the AIC criterion used by the Agency) almost as well as the Michaelis-Menten model, but exhibit rather different exposure-response relationships. The small dataset simply does not allow discrimination among models. Even as measured by the AIC, however, the Michaelis-Menten model is NOT the best fitting model as I discuss in the next bullet.
- Since the objective is to estimate a reference **concentration**, why does the Agency estimate an exposure-response relationship for **cumulative exposure**? An alternative approach would be to use concentration directly in the statistical analysis. Using the raw data provided by the Agency, I estimated the average concentration for each individual by dividing the cumulative exposure by duration of exposure and then fit a logistic regression model to the data with concentration as the measure of exposure. **This model (AIC = 73) fit the data equally well, or better than the Michaelis-Menten model (AIC = 74). The BMC and BMCL (using the BMDS software package distributed by the Agency) for this model were 0.06 and 0.04, respectively. Since the BMCL is obtained directly in terms of the concentration, it can be used as the point of departure (POD) for an RfC calculation without dividing by 60 (tantamount to adding a third uncertainty factor). With two uncertainty factors of 10 each, this procedure leads to an RfC of 0.0004, about 20 times larger than the RfC estimated by the Agency.**
- **Conclusion:** The data are too sparse to discriminate among models. A model based on concentration yields a better fit than the Agency preferred model and yields an RfC which is more than an order of magnitude lower than that estimated by the Agency. No matter which model is chosen, the sub-cohort used by the Agency should not be used for estimation of an RfC.

[1] BMCL is the lower 95% confidence limit on the benchmark concentration.

The evidence that pleural plaques represent an adverse clinical condition is tenuous at best

Over the years there has been considerable controversy regarding whether pleural plaques are simply a marker of asbestos exposure or whether they are associated with pulmonary deficiencies. Since asbestos exposure is associated with both pleural plaques and decreases in pulmonary function, any study that does not adjust adequately for asbestos exposure is likely to show an association between pleural plaques and decreases in pulmonary function. The SAB Panel identified for its and the Agency's consideration three recent papers on the association between pleural plaques and decreases in pulmonary function, two based on studies in the Libby population (Weill et al., 2011; Larson et al., 2012a) and one based on a study in France (Clin et al., 2011). These papers have attempted to adjust for exposure to asbestos, albeit with modest success. I review these studies here and conclude that any causal association between pleural plaques and decreases in pulmonary function is tenuous at best.

- Studies based on the population of Libby The Weill (2011) and Larson (2012a) studies were both based on the same data, which was collected by the ATSDR. Serious limitations of both studies are the facts that the readers of the X-rays were aware of the exposure status of the subject and no normal X-rays were randomly mixed in with the test X-rays, a practice that is common in studies of this type. Furthermore, precise exposure information was not available. Subjects were classified according to how many 'exposure pathways' they were exposed. Weill reports a small but statistically significant decrease in forced vital capacity (FVC) associated with pleural plaques among men but not among women. This analysis did not control for level of exposure, but Weill reports that he obtains similar results with Grace Workers excluded. A serious problem with this study is the inconsistency of the reported results. For example, Weill reports that his study cohort consisted of 4,524 individuals, but the numbers reported in various tables do not add to this total. In table 6, for example, in which the most important results are reported, there appears to be no consistency in the numbers of men and women in each of the smoking categories.
- Larson (2012a) reports results similar to those reported by Weill. However, Larson's study included a significant number of individuals exposed to non-Libby asbestos. He had no quantitative information on this exposure, which could have been substantial. Therefore, his control for level of exposure was even less precise than that of Weill who excluded subjects with other asbestos exposure. Moreover, his pleural plaque analysis includes individuals with parenchymal abnormalities, although he reports controlling for this in the statistical analysis. It would have been better to repeat the analyses with these individuals excluded. Larson notes also that over 70% of the participants in the study were either overweight or obese. With such a high prevalence of overweight individuals, a number of reported pleural plaques could actually have been pleural fat leading to misclassification of exposure. In a second study, Larson et al. (2012b) examined the association between exposure to Libby amphibole and decreases in pulmonary function among Libby miners and reported that although pleural plaques were significantly increased at cumulative exposures of 1 f/cc-y, restrictive lung disease (a hallmark of which is a decrease in FVC) was observed only at very high exposures (166 f/cc-y). The results of this Larson study would appear to be inconsistent with the study on pleural plaques and

pulmonary function. In summary, in view of the deficiencies in study design (readers not blinded, no normal X-rays mixed in), the very small effect estimates, the ability to adjust for level of exposure only crudely, and the very large exposures associated with loss of pulmonary function in the other Larson (2012b) study, I conclude that these studies provide at best weak evidence of a causal association between pleural plaques and decreases in pulmonary function.

- The Clin et al. (2011) French study This was a study based on high resolution CT (HRCT) scanning, not X-ray, and reported a small but statistically significant decrease in FVC associated with pleural plaques. However, exposures to asbestos could only be estimated and the group with pleural plaques included individuals with 'other abnormalities' not further defined.
- **Conclusion**: Taken together these studies provide only weak evidence of a causal association between pleural plaques and decreases in pulmonary function. Moreover, Weill et al. (2011) and Clin et al. (2011) consider the small reported decreases in pulmonary function to be clinically insignificant.

B. Inhalation Unit Risk (IUR) for Cancer (lung cancer and mesothelioma).

There are two fundamental questions regarding the derivation of the IUR by the Agency. First, is the IUR based on analysis of an appropriate dataset? Second, are the models and methods of analyses appropriate? The answer is no to both questions.

The dataset used by the Agency for estimation of the IUR for cancer is inappropriate.

There is an obvious dataset that should be used for the derivation of an IUR. This is the cohort of vermiculite miners at Libby analyzed by Larson et al. (2010). The Agency chose instead to analyze a greatly truncated sub-cohort of this cohort on the grounds that better exposure assessments were available in the sub-cohort. This is a poor choice for the following reasons.

- The full cohort has 111 deaths from lung cancer and 19 deaths from mesothelioma. The sub-cohort that the Agency analyzed has only 32 lung cancer deaths and 7 mesothelioma deaths. Issues of confounding and effect modification cannot be examined in this small sub-cohort. As Dr. Wayne Berman points out in his recently submitted comments to the SAB, there is much to be gained from analyses of the entire data. SAB Panel preliminary comments strongly advised the Agency to consider the entire data set and address exposure uncertainties using Monte Carlo techniques. I strongly endorse this advice.
- The sub-cohort selectively eliminates older individuals in the full cohort and thus the estimates of risk are based on younger individuals. As discussed below, there is evidence of strong effect modification of the lung cancer risk by age in this cohort, with relative risk (RR) reaching a peak and then dramatically declining. This phenomenon is discussed in some detail in my previous reports. Selectively eliminating older individuals in the cohort has the effect of biasing estimates of the lung cancer risk upwards.
- By drastically reducing the size of the dataset and selectively eliminating older individuals, the Agency has lost the statistical power to detect effect modification of lung cancer risk by age. Dr.

Peto has made the equivalent comment that the Agency has ignored the departure from proportionality of hazards in the data.

- The SAB Panel identified for its and the Agency's consideration the recent paper by Lenters et al. (2011), which, at first glance, might appear to support the Agency's contention that exposure measurement error always biases estimates of risk downward. However, the Lenters paper does not support this conclusion for the following reasons. First, the Lenters analysis uses cumulative exposure as the measure of exposure to asbestos. Cumulative exposure is generally a poor measure because both intensity of exposure and duration of exposure are important for both lung cancer and mesothelioma. Second, the Lenters paper ignores the strong effect modification of lung cancer RR by age, with the RR being substantially lower in older individuals. In fact, if the cohorts with better exposure measurement in the Lenters study are younger, then effect modification could explain the higher RRs in these cohorts. Finally, the theorem about non-differential covariate measurement errors leading to risk estimates biased towards the null is often misinterpreted. This statement, although widely repeated by epidemiologists, is incorrect. First, not only must the misclassification be non-differential, it must satisfy other conditions (e.g., Jurek et al., 2005) for the result to hold. Second, the statement applies to the expectation of the risk estimate, not to the value of the estimate from any single study. Thus, it is possible to have non-differential misclassification that satisfies all the required conditions but the result of a single study may actually overestimate the risk. As Jurek et al. (2005) state, "...exposure misclassification can spuriously increase the observed strength of an association even when the misclassification process is non-differential and the bias it produced is towards the null." Similar discussion is provided by Thomas (1995) and Weinberg et al. (1995).
- **Conclusion:** There is not a single good reason for the selection of the sub-cohort for estimation of the IUR. There are many good reasons for using the entire cohort.

The models used by the Agency for analyses of lung cancer and mesothelioma deaths are inappropriate.

- I know of no lung carcinogen for which cumulative exposure is a reliable determinant of risk. For cigarette smoking, exposure to asbestos, and exposure to radiation, lung cancer risk is determined by intensity of exposure, duration of exposure, and time since exposure stopped. Yet, the Agency has made no attempt to investigate and use models that would have allowed the explicit incorporation of these factors for the estimation of lung cancer risk in the Libby cohort. One approach, which I strongly recommend, is to use methods based on ideas of multistage carcinogenesis, such as the two-stage clonal expansion (TSCE) model, an approach endorsed by Dr. Kreibel[2]. The risk of mesothelioma is well-known to depend on intensity of exposure, duration of exposure, and time since exposure stopped. The Agency recognized this fact in 1986 when it adopted the Peto-Nicholson model. Yet, in this risk assessment the Agency has dropped this model in favor of a model that makes no biological sense. Clearly, the decision

[2] I am mystified by Dr. Kreibel's recommendation that the Agency adopt the Richardson rather than the Moolgavkar approach since Richardson got his software code from my group. Furthermore, the code used by Richardson is dated and we now have more efficient ways of fitting the model with time-dependent exposures.

to jettison a large part of the data makes it impossible to fit the Peto-Nicholson model, which provides further justification for using the full cohort.

- The model used for analyses of lung cancer deaths completely ignores the strong effect-modification by age. Particularly because ultimately the IUR is based on a life-table analysis it is important to estimate and use age-specific RRs.
- **Conclusion**: For both lung cancer and mesothelioma, the Agency needs to use the entire Larson cohort, and investigate explicitly intensity and duration of exposure in determining risk. In addition, for lung cancer, the Agency should explore effect modification by age and use age-specific RRs for estimation of IUR.

RECOMMENDATIONS TO THE AGENCY

1. Abandon the attempt to derive an RfC for Libby amphibole. A suitable dataset does not appear to be currently available. If the Agency feels obligated to estimate an RfC, this estimate should be based on the full Rohs dataset and a realistic biological model should be used.
2. The IUR for cancer should be based on the entire Larson cohort, the roles of intensity of exposure and duration should be explored using models based on ideas of multistage carcinogenesis, and, for lung cancer, the strong effect modification by age should be recognized and incorporated in the estimation of IUR.
3. It is incumbent upon the Agency to discuss the carcinogenic potency of Libby amphibole in relation to the potencies of other asbestos fibers. The Agency argument that such a discussion could be highly controversial is not convincing. This is not like the 'amphibole hypothesis', which has been hotly debated. In fact, analyses of the Libby miners' data have provided us with solid estimates of the potencies of Libby amphibole for lung cancer and mesothelioma. The analyses by Hodgson & Darnton (2000) and Berman & Crump (2008a, b) provide us with a range of estimates for other asbestos fibers. It is clear that the potency of Libby amphibole for mesothelioma lies somewhere in the middle of the range and is approximately half the potency assumed by the Agency in its 1986 asbestos risk assessment. For lung cancer, the potency of Libby amphibole is rather low compared to other asbestos fibers, considerably lower than the potency assumed by the Agency for its 1986 risk assessment. As it is, the general perception is that Libby amphibole is much more toxic than other asbestos fibers. It is time for the Agency to dispel this myth, at least for cancer risks.

References

Berman, WD, and KS Crump. 2008a. Update of potency factors for asbestos-related lung cancer and mesothelioma. Crit Rev Toxicol 38(S1):1-47.

Berman, WD, and KS Crump. 2008b. A meta-analysis of asbestos-related cancer risk that addresses fiber size and mineral type. Crit Rev Toxicol 38(S1):49-73.

Clin, B, F Morlais, G Launoy, A-V Guizard, B Dubois, V Bouvier, N Desoubeau, M-F Marquignon, C Raffaelli, C Paris, F Galateau-Salle, L Guittet, and M Letourneux. 2011. Cancer incidence within a cohort occupationally exposed to asbestos: A study of dose-response relationships. Occup Environ Med 68:832-836.

Hodgson, JT, and A Darnton. 2000. The quantitative risks of mesothelioma and lung cancer in relation to asbestos exposure. Ann Occup Hyg 44(8):565-601.

Jurek, AM, S Greenland, G Maldonado, and TR Church. 2005. Proper interpretation of non-differential misclassification effects: Expectations vs observations. Int J Epidemiol 35:680-687.

Larson, TC, VC Antao, and FJ Bove. 2010. Vermiculite worker mortality: Estimated effects of occupational exposure to Libby amphibole. J Occup Environ Med 52(5)555-560.

Larson, TC, M Lewin, EB Gottschall, VC Antao, V Kapil, and CS Rose. 2012a. Associations between radiographic findings and spirometry in a community exposed to Libby amphibole. Occup Environ Med (forthcoming).

Larson, TC, VC Antao, FJ Bove, and C Cusack. 2012b. Association between cumulative fiber exposure and respiratory outcomes among Libby vermiculite workers. J Occup Environ Med 54(1):56-63.

Lenters, V, R Vermeulen, S Dogger, L Stayner, L Pertengen, A Burdorf, D Heederik, and National Institutes of Environmental Health Sciences (NIEHS). 2011. A meta-analysis of asbestos and lung cancer: Is better quality exposure assessment associated with steeper slopes of the exposure-response relationships?. Environ Health Perspect 119(11):1547-1555.

Rohs, AM, JE Lockey, KK Dunning, R Shukla, H Fan, T Hilbert, E Borton, J Wiot, C Meyer, RT Shipley, GK LeMasters, and V Kapil. 2008. Low-level fiber-induced radiographic changes caused by Libby vermiculite. Am J Respir Crit Care Med 177:630-637.

Thomas, DC. 1995. Re: 'When will nondifferential misclassification of an exposure preserve the direction of a trend?' Am J Epidemiol 142:782-783.

Weill, D, G Dhillon, L Freyder, J Lefante, and H Glindmeyer. 2011. Lung function, radiological changes and exposure: Analysis of ATSDR data from Libby, MT, USA. Eur Respir J 38(2):376-383.

Weinberg, CR. DM Umbach, and S Greenland. 1995. Weinberg et al. reply. Am J Epidemiol 142:784.

APPENDIX B – 7

ADDITIONAL COMMENTS ON THE DRAFT RISK ASSESSMENT FOR LIBBY AMPHIBOLE WITH EMPHASIS ON RE-ANALYSES OF THE RESTRICTED ROHS COHORT FOR DERIVATION OF A REFERENCE CONCENTRATION

SURESH H. MOOLGAVKAR, M.D., Ph.D.

April 23, 2012

These comments constitute an addendum to the comments I posted on the Science Advisory Board (SAB) website in March, 2012, and are based on extensive re-analyses of the sub-cohort used by the U.S. Environmental Protection Agency (the Agency) for the estimation of an RfC for Libby amphibole. The focus of these comments is a discussion of my re-analyses of this dataset. In addition, I respond in these comments to some of the recommendations made by the SAB to Administrator Jackson in a draft letter dated April 4, 2012.

I have done extensive re-analyses of the dataset used by the Agency for the estimation of an RfC for Libby amphibole. This dataset is a subset of the data analyzed by Rohs et al. (2008) and includes 118 workers with 12 cases of pleural plaque. These re-analyses show that the dataset is far too small for reliable estimation of an RfC . I believe also that the Agency used an inappropriate model, the Michaelis-Menten model, for estimation of the RfC.

The Michaelis-Menten Model

This model has been widely used to study receptor binding and enzyme kinetics. In its original form, used for the analyses of enzyme kinetics, the model has only two parameters. The model has been extended by the Agency to include a third parameter. In the Agency formulation, the three parameters that can be estimated from the data are a background, a plateau, and a parameter, which I will call the 'slope'.

- The background parameter is an estimate of the fraction of the general (unexposed) population that has pleural plaques.
- The plateau estimates the fraction of 'susceptible' individuals in the population. If the plateau is below 100%, it implies that a certain fraction of the population will never develop pleural plaques no matter how large the exposure to asbestos, a dubious biological construct.
- Finally, the 'slope'[1] determines how steep the exposure-response relationship is, i.e., how quickly the exposure-response curve rises from the background to the plateau.
- **It is clear that if the plateau is equal to the background, then there is no evidence of an exposure-response relationship in the data.**

Estimating the RfC using the Michaelis-Menten and other models

I have re-analyzed the dataset provided by the Agency using both Michaelis-Menten models and logistic regression models, which are more traditional in benchmark dose analyses. For the Michaelis-Menten analyses, I used the approach described by the Agency in its draft risk

[1] The third parameter influences the speed with which the exposure-response curve approaches the plateau, but is not actually the slope in the strict mathematical sense. The slope of the exposure-response curve is not a constant and is a complicated function of all three parameters.

assessment for Libby amphibole, including the use of profile-likelihood-based lower confidence intervals for estimation of the BMCL[2]. I used the BMD software (BMDS) available from the Agency website for the logistic regression analyses. This software also uses profile likelihoods to estimate the BMCL. I confirmed that my model results were identical to those reported by the Agency for the same models. Here are my observations:

1. Although it is possible to estimate all three parameters even in this sparse dataset, the Agency fixed the background rate of pleural plaques at 1% with little justification, and estimated only the plateau and the slope. When all three parameters are estimated from the data, the estimate of background rates varies between 3 and 4.5% depending upon the lag structure chosen for the exposure[3].
2. Although I did not test directly the hypothesis of equality of background and plateau in the three-parameter models, the large standard errors I found for each of these parameters suggest that equality of these two parameters cannot be rejected indicating that these data provide little evidence of an exposure-response relationship between cumulative exposure and prevalence of pleural plaques.
3. I tried a number of two-parameter Michaelis-Menten models (background rates fixed) with different lags for exposure and with various assumptions regarding the background rates of pleural plaques. With a ten-year lag and with the assumption that the background rate is 1% (this is the Agency's chosen model), I estimated a BMCL of 0.1178, identical to the BMCL reported by the Agency. As expected, however, the estimate of BMCL depends both on the chosen lag structure and the assumed background rate. These results are shown graphically in figure 1 below.
4. In every one of the Michaelis-Menten models I used to analyze the data, the estimated standard error for the plateau is so large that the hypothesis that the plateau is equal to the background cannot be ruled out by the standard Wald test[4]. **If the Agency insists on using the Michaelis-Menten model, it is incumbent upon the Agency to show that the plateau is statistically significantly different from the background. If the hypothesis of equality of background and plateau cannot be rejected, then the Agency should recognize that the model fails to find an increase in response (pleural plaques) with increasing exposure.**
5. In addition to the Michaelis-Menten model, I have analyzed the data using logistic regression models with both cumulative exposure and average concentration[5] (cumulative exposure divided by duration of employment) as the measure of exposure.

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[2] This is the lower 95% confidence limit on the benchmark dose or benchmark concentration.
[3] By the AIC criterion, the fit of the Michaelis-Menten model is worse when all three parameters are estimated in the data used by the Agency.
[4] The Agency should develop a likelihood-based test for this hypothesis.
[5] I use the terms concentration and intensity interchangeably in this document.

The concentration-response models, in particular, fit the data as well as, or better than, the Michaelis-Menten models as judged by the AIC. However, these two classes of model (Michaelis-Menten and logistic) predict very different shapes for the exposure-response curves. This finding suggests very strongly that this sparse dataset does not allow discrimination among models and is, therefore, unsuitable for the estimation of an RfC. Figure 2 shows the exposure-response relationships for some Michaelis-Menten and logistic regression models. As judged by the AICs shown in that figure, the logistic regression concentration-response models describe the data best. SAB member Dr. Sheppard suggests that a supra-linear exposure-response relationship is biologically plausible and has been observed in other contexts, such as the impact of particulate matter on cardiovascular mortality. Be that as it may, the data at issue here are too sparse to distinguish between supra-linear and sub-linear models.

6. An examination of the raw data by deciles of exposure (Table 1) also indicates that there is little evidence of a supra-linear relationship between cumulative exposure and pleural plaques. This table makes it very clear that exposure-response relationships are driven largely by the number of pleural plaques in the highest decile of cumulative exposure.
7. Because the Agency uses cumulative exposure in its analyses of the data, it divides the estimated BMCL by 60 to derive a concentration adjusted for a 70-year lifetime. The Agency then uses two safety factors of 10 each to arrive at an estimate of the RfC. In my opinion, this procedure is tantamount to using three safety factors. If the BMCL is derived for the concentration directly, then two safety factors of 10 each can be applied directly to this BMCL. For example, with lag zero, the logistic concentration-response model (see figure 1) has an AIC of 73.0 (and therefore describes the data better than the Agency preferred Michaelis-Menten model with an AIC of 74.0) with BMCL = 0.04. Using this BMCL as the point of departure and using two safety factors of 10 each yields an RfC = 0.0004, which is 20 times the RfC estimated by the Agency.

Decile	Exposure (f/cc-yr)	Cases	Subjects	Prevalence
1	0.02	1	12	0.08
2	0.04	0	12	0.00
3	0.07	1	12	0.08
4	0.09	0	12	0.00
5	0.11	0	11	0.00
6	0.14	1	12	0.08
7	0.22	2	12	0.17
8	0.32	2	12	0.17
9	0.50	1	12	0.08
10	2.29	4	11	0.36

Table 1: Rohs restricted data set divided into deciles with even numbers of exposed subjects. The second column labeled "Exposure" is the average cumulative exposure lagged 10 years in each decile. It is absolutely clear that there is no evidence of an increase in the prevalence of pleural plaques with increasing cumulative exposure except in the highest decile.

Comments on SAB recommendations regarding the RfC

With respect to the RfC, "[t]he SAB recommends that EPA include any X-ray abnormalities (localized pleural thickening, diffuse pleural thickening, or asbestosis) as the health outcome." There are no reported cases of asbestosis in the database used by the Agency for derivation of the RfC. The definition of asbestosis requires demonstration of substantial exposure to asbestos. The SAB appears to be suggesting that all cases of interstitial fibrosis in the data be called "asbestosis" and included in the analyses. In my view this would be totally inappropriate. Pleural plaques are at least considered to be markers of asbestos exposure. In contrast, it is well known that there are many causes of interstitial fibrosis other than exposure to asbestos, a significant fraction of cases of interstitial fibrosis is idiopathic, and age is a strong risk factor for the development of this condition. Control of confounding would be particularly problematic if interstitial fibrosis were included in the analyses. Accordingly, this recommendation is inappropriate and should be withdrawn.

I take issue also with the SAB conclusion that use of the full cohort of 434 workers for confirmatory analyses is reasonable. Rohs et al. (2008) gave excellent reasons for including only a subset of 280 individuals from the original cohort of 434 workers for their analyses. I believe that, if pleural plaques are to be used for the derivation of an RfC, then the sub-cohort analyzed by Rohs et al. (2008) is the most appropriate dataset to use.

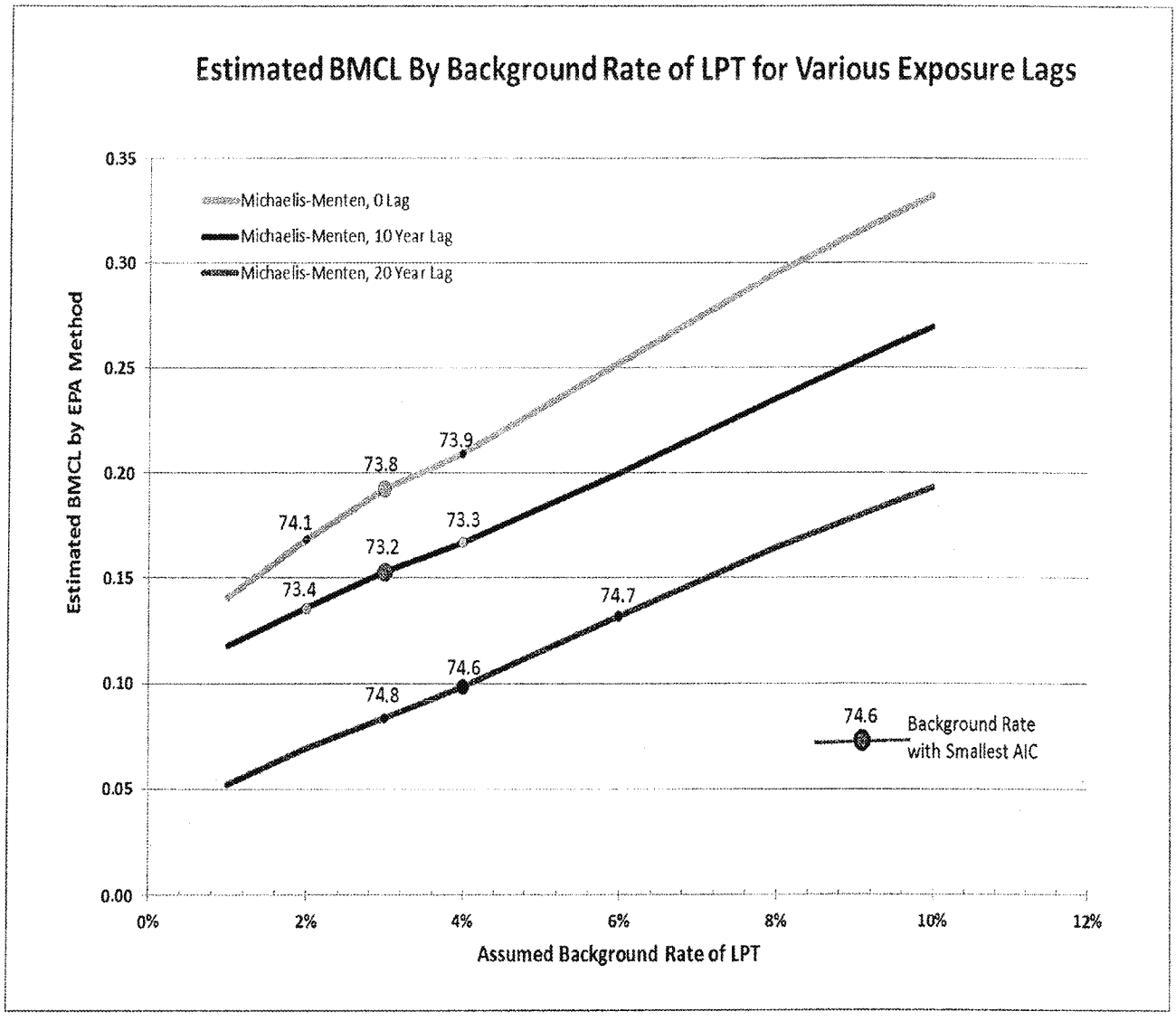

FIGURE 1: Estimated BMCLs using the Michaelis-Menten models. Estimated BMCL depends on both the lag structure for cumulative exposure and on the assumption regarding background rates of pleural plaques. For each lag (0, 10 and 20 years), the AICs are shown for various ass assumed background rates, with the lowest AIC highlighted. Note that all models describe the data about equally well.

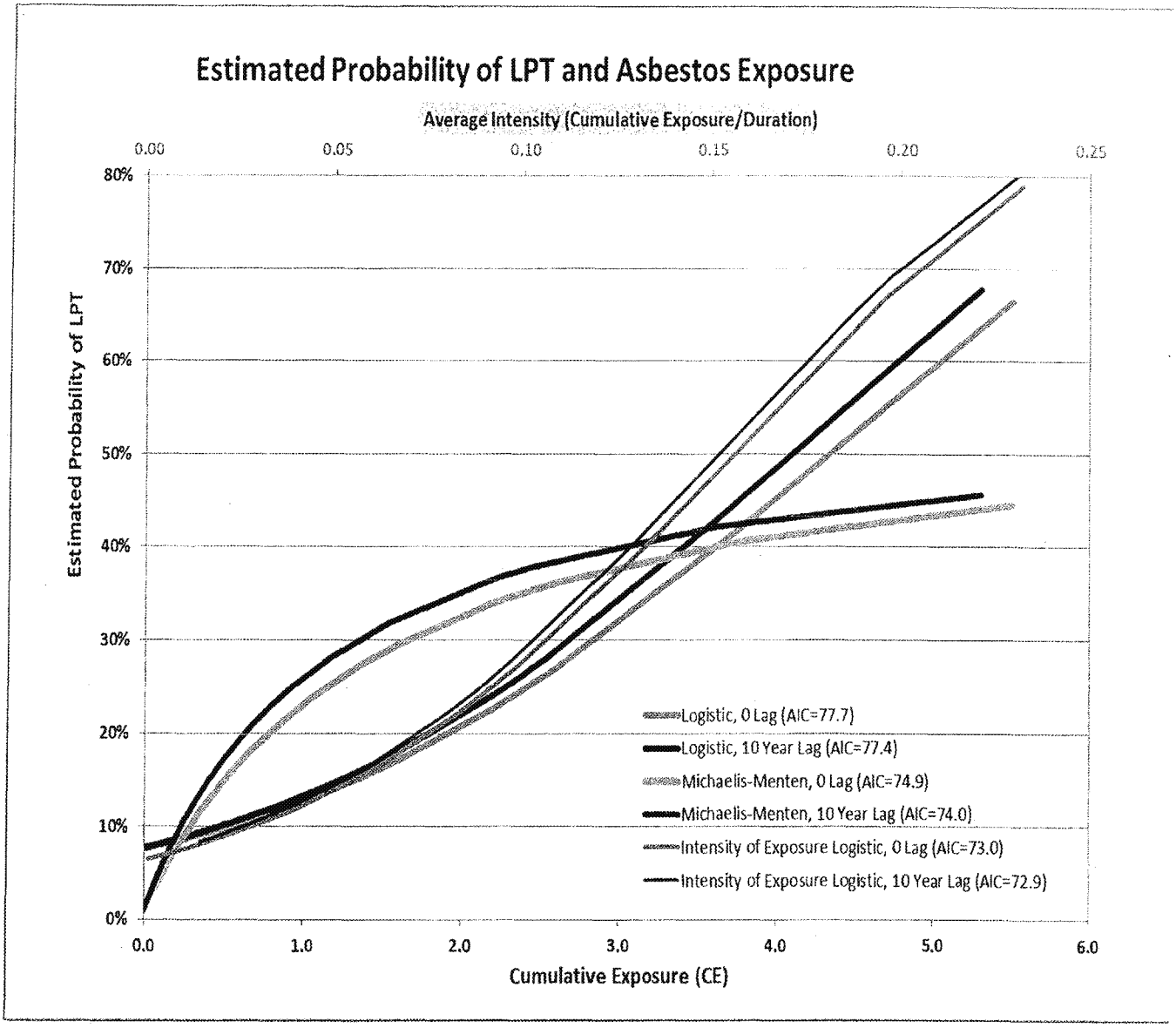

FIGURE 2: Dose-response relationships using Michaelis-Menten and logistic regression models. The two (supra-linear) curves to the left are outputs of Michaelis-Menten models with zero (AIC = 74.9) and 10 year (AIC = 74.0) lags for exposure. The four sub-linear curves to the right are outputs of logistic regression models, two with cumulative exposure as the measure of exposure, and two with average concentration (intensity) as the measure of exposure. Note that by the AIC, the sub-linear concentration-response models describe the as well as, or better than, the EPA chosen model (Michaelis-Menten with 10 year lag). Note also that when all three parameters for the Michaelis-Menten model are estimated from the data, the fit as judged by the AIC becomes worse. Therefore, the logistic concentration-response models are clearly superior.

Recommendations to the Agency

1. Much better justification is required before pleural plaques can be used as an end-point for derivation of an RfC. The inclusion of all X-ray abnormalities as an end-point makes little biological sense because the potential confounders for pleural plaques are different from those for interstitial fibrosis.
2. The dataset used by the Agency for the estimation of an RfC is too small to distinguish among models with very different exposure-response relationships. If the Agency insists on using pleural plaques for the derivation of an RfC, then a more appropriate and larger dataset should be used. The data used by Rohs et al. (2008) is a possible candidate.
3. The use of the Michaelis-Menten model needs to be better justified. What is the interpretation of the plateau? Why should a fraction of the population be immune to the effects of exposure?
4. The Michaelis-Menten model is a three-parameter model. In the absence of reliable information on the background rate of pleural plaques, all three parameters should be estimated from the data. The Agency needs to provide the appropriate analyses to show that in their preferred Michaelis-Menten model, the plateau is statistically significantly different from the background.
5. I endorse the recommendation made by the SAB Panel that the Agency analyses used for the derivation of the Inhalation Unit Risk (IUR) for cancer be extended by using models based on ideas of multistage carcinogenesis. I recommend that these extended analyses be done for both lung cancer and mesothelioma. These analyses will allow the exploration of the temporal aspects of risk following exposure to Libby amphibole. In addition to the analyses based on multistage carcinogenesis, I recommend also that the temporal aspects of risk in lung cancer be explored using conventional statistical approaches, such as the Cox model with flexible spline smoothers to investigate effect modification by age.
6. I do not agree with the SAB Panel that the Agency has chosen the appropriate dataset for the analyses. In fact, the dataset was expressly chosen to eliminate effect modification by age. Therefore, I believe that the entire Libby cohort with follow-up through 2006 should be used for estimation of the IUR. Uncertainties in exposure estimates should be addressed via monte-carlo simulations.
7. The SAB Panel appears to recommend that the algorithms used by Richardson (2008) and Zeka et al. (2011) be used to fit the data using the two-stage clonal expansion (TSCE) model. I would like to inform the Agency that better algorithms and software than those used in these publications have been developed. I would recommend using

APPENDIX B – 8

COMMENTS ON PANEL RECOMMENDATIONS TO EPA REGARDING THE DRAFT RISK ASSESSMENT OF LIBBY AMPHIBOLE ASBESTOS – JULY 2012

Suresh H. Moolgavkar, M.D., Ph.D.

Exponent, Inc.

I have reviewed carefully the most recent version of the draft SAB panel report on EPA's draft Libby Amphibole Asbestos IRIS assessment. Although appreciative of the panel's ongoing efforts, I am once again disappointed that the panel has not seen fit to respond to many of the fundamental scientific issues and concerns raised in earlier public comments. The latest revised report of the panel continues to support EPA positions of dubious scientific validity, and makes assertions that are simply incorrect. The panel should discuss and rectify these errors before sending its report to the full SAB for further review.

Issues arising in the derivation of the RfC

- The panel continues to support the use of pleural plaques or localized pleural thickening ("LPT") as the appropriate non-cancer endpoint for the derivation of an RfC, asserting that this condition is predictive of "risk for other asbestos-related diseases, including asbestosis, mesothelioma and lung cancer." The panel needs to clarify what exactly it means by this assertion. Adenomatous polyps of the colon are predictive of the risk of colon cancer because they lie on the pathway to disease, i.e., they represent an intermediate stage on the pathway to colon cancer. Urinary cotinine levels are predictive of lung cancer because they reflect smoking habits, but elevated cotinine levels are not on the pathway to lung cancer. Similarly, dicentrics in lymphocyte chromosomes from radiation exposures are clearly specific indicators of radiation exposure and thus measures of increased cancer risk but are in themselves not biological cancer risk factors since cells with unstable chromosome aberrations such as dicentrics will not divide. Is the panel asserting that pleural plaques are on the biological pathway to more serious pulmonary disease? Or is the panel saying, as some panel members have appeared to state during the panel's deliberations, that pleural plaques are simply markers of asbestos exposure and therefore correlated with more serious pulmonary disease? If the former, what is the evidence that, *conditional on asbestos exposure*, pleural plaques are associated with serious pulmonary disease? There is very little evidence of which I am aware to support the conclusion that pleural plaques lie on the biological pathway to serious pulmonary disease and the revised draft report does not appear to cite to any. If the panel has concluded that LPT is on the biological pathway to pulmonary disease, it is incumbent upon the panel to cite to the scientific literature supporting that conclusion. If, on the other hand, pleural plaques are simply markers for asbestos exposure, then their use for derivation of the RfC is highly questionable.
- The panel continues to assert that pleural plaques are associated with decreases in pulmonary function without a thorough evaluation of the literature. As noted in my previous comments, none of the papers cited in support of this proposition provides convincing evidence that pleural plaques are associated with decreases in pulmonary function *conditional on asbestos exposure.*
- The panel continues to make the ill-advised recommendation that all X-ray abnormalities be included for the derivation of the RfC. Employing endpoints that may have different sets of confounders is scientifically unsound. There is general agreement that small opacities are

associated with cigarette smoking. Suggesting that asbestosis be included is even more unsound because asbestosis is not a radiographic diagnosis. The X-ray may suggest the existence of pneumoconiosis, which can be caused by many exposures in addition to asbestos. Suggesting that these disparate X-ray abnormalities be combined into a single endpoint for analyses is akin to suggesting that lung cancer and mesothelioma be analyzed together as a single cancer endpoint.

- Despite the panel's clear concern for the paucity of data upon which EPA has based its proposed RfC, the draft report continues to support the use of a small subset of the original Marysville cohort for derivation of the RfC. The panel has completely ignored the analyses I presented in my previous comments that this data set has no power to discriminate among models. Furthermore, the panel recommends that the entire Marysville dataset be used for sensitivity analyses despite considerable missing information. Instead, the subset used in Rohs et al. (2008) should be utilized for this purpose. As Rohs et al. (2008) point out, of the original members of the cohort, only 280 had both readable chest X-rays and complete interviews. Since evaluation of possible confounders should be an important objective of sensitivity analyses, it is more scientifically sound to use the Rohs sub-cohort for the sensitivity analyses than the entire original cohort.
- On page 27, the panel recommends "a thoughtful approach to model selection..." I endorse this recommendation, but am at a loss to understand exactly what the panel is recommending. How does the panel expect EPA to develop a model based on "...considerations of biological/epidemiologic plausibility.." when it is relying on a miniscule dataset? How does the panel expect EPA to examine "local smoother estimates from the data" in this small dataset? To enhance the clarity of its recommendations, the panel should address these questions. Ultimately, the panel recommends use of the dichotomous Hill model. This model is no more "biologically plausible" than the Michaelis-Menten model. These models were first developed for quantitative descriptions of enzyme kinetics and receptor binding and have no foundation in epidemiology. The feature that distinguishes them from the more conventional logistic regression models is that the exposure-response relationship with these models is supra-linear in the low-dose region, rather than sub-linear as with logistic regression. Use of the dichotomous Hill model is no more scientifically justified in this context than use of the Michaelis-Menten model. In fact, the dichotomous Hill model requires the estimation of 4 parameters, one more than the Michaelis-Menten model. In order to fit this model to the small data set, the panel is recommending that EPA fix the values of the background probability of pleural plaques at 1% (as it does for the Michaelis-Menten model) and, in addition, fix the plateau at 85%. Thus, in a giant step backwards, the panel is recommending that the Agency fix two parameters at highly uncertain values.

Issues arising in the derivation of the IUR

- The panel continues to support use of the sub-cohort of workers employed after 1959 as the primary dataset for the derivation of the IUR, but fails to note the limitations of this dataset. While it is true that exposure information was missing on many of the workers hired before

1959, exclusion of these workers excludes many of the older individuals in the cohort when lung cancer, in particular, is most common. As I have pointed out in my previous comments, there is strong evidence of effect-modification by age in the Libby lung cancer data. This finding is consistent with that reported by Richardson in the North Carolina Textile Workers cohort. By eliminating many of the older individuals, the post-1959 dataset does not allow the investigation of effect-modification by age at Libby. Since the estimated IUR is based on a life-table analysis, it is particularly important that effect-modification by age be investigated and age-specific relative risks be used if at all possible. Although various members of the panel appear to have concurred that additional pre-1959 data can and should be used, the revised draft report makes no clear recommendation to that effect. For the above-state reasons, it should. For mesothelioma, use of the post-1959 dataset leads to a drastic reduction in the number of mesotheliomas used in the analyses. The small number (7) of mesotheliomas in the post-1959 data precludes a proper analysis. In a giant step backwards, the Agency analyzes these data using Poisson regression with cumulative exposure as the measure of exposure. This model for exposure-response flies in the face of all we know about the epidemiology of mesothelioma. The Peto-Nicholson model shows that mesothelioma risk depends independently on intensity and duration of exposure with the incidence being a linear function of concentration and a power function of duration of exposure. This model has been shown to be a good description of mesothelioma incidence in many occupational cohorts (Berman and Crump, 2008). The current asbestos IUR in IRIS recognizes that mesothelioma risk is NOT a function of cumulative exposure. Not to do so in this risk assessment would be a travesty.

- The panel recommendation for investigating the temporal aspects of disease risk is one that I heartily endorse. I would recommend that the panel request EPA go further and explore the temporal aspects of both exposure and risk. The best approach to doing so is to use exposure-response models based on ideas of multistage carcinogenesis. The panel recommends using the TSCE model. I concur. It is important, however, that the exact stochastic solution to the model be used, not deterministic approximations. The panel should make that clear in its report.
- In several locations in its revised draft, the panel refers to linearity of exposure-response relationships for amphibole-associated carcinogenesis, suggesting that there is limited evidence to support said linearity. Such statements are, at best, totally misleading and, at worst, completely wrong. The panel needs to be much more explicit as to what it means. What is the 'response' under consideration? What is the measure of exposure? There are currently two widely recognized exposure-response models for mesothelioma, the Peto-Nicholson model (for incidence) and the Hodgson-Darnton model (for life-time risk). Neither is linear with cumulative exposure as a measure of exposure. As noted above, the Peto-Nicholson model cannot even be expressed in terms of cumulative exposure. The Hodgson-Darnton model is couched in terms of cumulative exposure, but is not linear. For lung cancer, the Cox model is log-linear, not linear. Often a linear ERR (excess relative risk) model, in which the ERR is expressed as a linear function of cumulative exposure, is used to analyze the data. Howeverit provides a poorer description of the data than models like the TSCE model, in which the entire history of exposure is used rather than summary measures, such as cumulative exposure. The panel should either remove or revise loose statements regarding linearity from its report.

Recommendations

- The panel should recommend that EPA abandon for now the attempt to derive an RfC for Libby amphibole. In the absence of a suitable dataset, derivation of an RfC is unsupportable as a matter of sound science If the panel continues to endorse the use of pleural plaques as the appropriate endpoint, it should provide stronger support for its assertion that pleural plaques are predictive of more serious pulmonary disease and decrements in pulmonary function.
- The IUR for cancer should be based on the entire Larson dataset or, at the very least, detailed sensitivity analyses based on the full cohort should be undertaken. I endorse the use of the TSCE model for lung cancer analyses providing the exact stochastic solution is used and temporal aspects of exposure and risk, including effect-modification by age, are carefully investigated. For mesothelioma, the Peto-Nicholson model, or some variant of it should be used, at least in the sensitivity analyses. These are fundamental substantive issues. The panel should not get hung up on issues of little or no importance, such as possible correlations between lung cancer and mesothelioma in the data. There is no evidence that, conditional on exposure, there is any correlation between these two outcomes. The panel should revise ill-advised, general statements in the draft report regarding linearity of risk associated with amphibole asbestos, as outlined above.
- As I recommended in my earlier comments, the risk associated with exposure to Libby amphibole should be discussed in the context of risks associated with other amphiboles. There is sufficient information to do so for the carcinogenic potency. This task is relatively straightforward given the publications of Hodgson and Darnton (2000) and Berman and Crump (2008a,b), and can be done without getting into controversial issues. Doing so would enhance the public's understanding of the relative risks of various amphiboles.
- To enhance the transparency of its conclusions and further assist EPA, the panel should ensure that the cover letter to the EPA Administrator is revised to reflect all the central recommendations that the panel's report ultimately makes.

ONE FURTHER COMMENT FOLLOWING THE CONFERENCE CALL ON JULY 25, 2012

SURESH H. MOOLGAVKAR

I would like to point out to the Panel that it is logically inconsistent to say that the Michaelis-Menten and dichotomous Hill models are simply mathematical descriptions of the pleural plaque data without any biological and epidemiological interpretation and then to use the probabilities for background and plateau from epidemiological data. You cannot have it both ways.

APPENDIX B – 9

Statement for Public Teleconference for the SAB review of "Draft Toxicological Review of Libby Amphibole Asbestos" (EPA/635/r/002a)

David G. Hoel, Ph.D.
Exponent, Inc.

May 1, 2012

Prior Comments

1. Additional Comments from Elizabeth Anderson and David Hoel, Exponent, Inc., (04/09/2012)
   - Selection of critical endpoint
   - Derivation of draft RfC
   - Practical considerations

Exposure Response Models for Pleural Plaque Prevalence: Michaelis-Menten:

- Michaelis-Menten models the rate of an enzyme-catalyzed reaction of a single substrate, which is a function of the substrate concentration.
- This is a saturable process and thus is unlikely to have anything to do with the prevalence of pleural plaques resulting from asbestos exposures.
- The model has been changed to add a background prevalence term. Since without any substrate the model then will still have a reaction. Since this makes little sense the modified Michaelis-Menten model should be considered to simply be a non-linear function that is used in a curve fitting exercise.
- The background parameter is set at 1% instead of being estimated from the data. This artificially reduces the AIC value. It would be increased by 2 if the background value was indeed estimated to be 1 from the data. This then gives the modified model an unfair advantage over the other competing models from an AIC standpoint.

Exposure Response Models for Pleural Plaque Prevalence: Hill Model:

- Hill Model models the fraction of occupied sites on a macromolecule by a ligand as a function of the ligand concentration. It estimates the degree of cooperation in the reaction either positive of negative by occupied sites.
- It should be noted that the logit of the fraction of occupied sites is linear in the concentration of the ligand and the log of the dissociation constant (which equals the ligand concentration at ½ occupancy raised to the nth power where n is the Hill parameter). Therefore a simple logistic regression is equivalent to using the Hill model.
- As with the Michaelis-Menten model the Hill model is converted in the analysis into something else by adding a saturation parameter as well as a non-estimated background parameter. The same argument applies to using AIC for model comparisons with other functions which do not include a non-data estimated parameter.

Exposure Response for Pleural Plaque Prevalence:

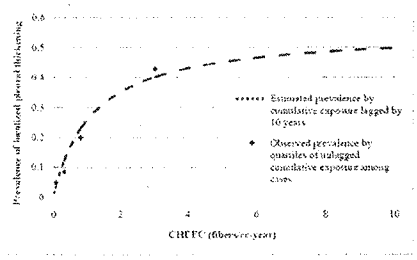

Figure 1. EPA's dose-response model fit for pleural thickening versus raw data in quartiles of cases (Figure E-1 in EPA Draft Toxicological Review)

Exposure Response for Pleural Plaque Prevalence:

- The data used for the curve fitting consists of only 4 data points with some of the models having 3 parameters needing to be estimated. This does seem to approach over-parameterization.
- In determining the 4 data points the exposure intervals are defined by the outcome variable i.e. 3 pleural plaques per exposure interval. The independent variable being the average exposure in the interval is thus also a dependent variable which makes for an interesting error structure in using typical regression methods. This should be discussed.

Exposure Response for Pleural Plaque Prevalence:

- The previously given Figure 1 illustrates the limited nature of the data using intervals based on the number of subjects which is usual instead of defining the intervals by outcome. This also illustrates the very limited nature of model fitting with only 12 outcomes. Also known modifying factors such as BMI and age will not be able to be included because of the limited data.

Table 1. Rohs restricted data set divided into quartiles with even numbers of subjects

Quartile	Exposure (f/cc-yr)	Cases	Subjects	Prevalence
1	0.033	2	29	0.069
2	0.092	0	30	0.000
3	0.20	3	29	0.103
4	1.1	7	30	0.233

Exposure Response for Pleural Plaque Prevalence:

- The background rate that is assumed to be equal to 1% is an interesting modeling assumption. Pleural plaque prevalence appears to increase with age and has been estimated in the U.S. using NHANES II by Rogan et al. (2000) (see EPA section 5.3.2.2). The reported prevalence for males 45-74 was 7.8% which is quite high for the U.S. considering the 1% assumption. When the preferred modified Michaelis-Menten model was run allowing for background prevalence estimation (estimated at 3.12%) the resulting AIC value was not reported.

Exposure Response for Pleural Plaque Prevalence:

- Using the full Rohs data set restricted to employment beginning at least 20 years prior to screening there are 293 workers. The screening reported 73 workers with pleural plaques and 11 with diffuse pleural thickening.

- None of the cases of pleural thickening had pleural plaques indicating the concept that the plaques are not in the disease pathway of pleural thickening.

- Recommendation:

  Apply simple and well understood dose-response models such as logistic regression instead of using biochemical models that are scientifically misleading by being unrelated to the prevalence of pleural plaque formation from asbestos exposures and having been modified in such a way that they are no longer biochemical models.

APPENDIX B – 10

Comments from Dr. David Hoel, 7/23/2012

The SAB has not in my opinion given an adequate review of the proposed RfC methods given in the EPA document. Dr. Suresh Moolgavkar has clearly expressed the failings of the review on a number of important issues and for which I totally concur with his conclusions. To reiterate several points that I had offered previously the following should be considered by the SAB.

- The most scientific questionable position taken by the SAB is that pleural plaques (localized pleural thickening) are "predictive of risk for other asbestos-related diseases, including asbestosis, mesothelioma, and lung cancer." Arguably, plaques are biomarkers of asbestos exposure but is there any evidence that they are biologically involved with lung cancer? Other well known markers of exposure such as the presence of dicentrics in lymphocyte chromosomes from radiation exposures are clearly specific indicators of radiation exposure and thus measures of increased cancer risk but are in themselves not biological cancer risk factors since cells with unstable chromosome aberrations such as dicentrics will not divide.
- The reference to biochemical models such as Michaelis-Menten and the Hill model is most inappropriate in that it gives a false sense of scientific credibility to a simple curve fitting activity. The formation of pleural plaques has nothing to do with these two biochemical reaction models and as such the impression that they do should not be given. A less deceptive approach would to be to use simple polynomial regression or logistic regression which is the same statistically as the Hill model.
- The EPA model assumed a plateau of pleural plaque formation of 56% in a population while data has shown 85% among some worker groups. Using a value less than 100% requires some biological explanation since it is not clear that there is a percentage of individuals will never have a pleural plaque no matter what are their exposure rate and duration of exposure. In other words they are somehow genetically or otherwise immune. The SAB should justify biologically why they recommend that a value less than 100% be used by EPA and that the value is to be obtained from some study found in the open literature.
- The SAB discusses that cigarette smoking is not an issue with respect to pleural plaques. No mention is however given to BMI and its association with false positive radiograph findings. Further BMI is also associated with pulmonary function deficits which in turn relates to the SAB's conclusion that pleural plaques cause pulmonary function effects.
- Using a single small data set to derive an RfC or RfD is generally inappropriate. Estimated values should be obtained from many other data sets and compared.

APPENDIX B – 11

COMMENTS TO THE SAB ON THE PANEL RECOMMENDATIONS ON THE EPA DRAFT RISK ASSESSMENT FOR LIBBY AMPHIBOLE ASBESTOS

David Hoel

Suresh Moolgavkar

September 18, 2012

We have been following the EPA risk assessment process for Libby amphibole asbestos (LAA) and have made detailed comments to the special SAB panel set up to review the first EPA draft of the risk assessment. We have a number of concerns that were laid out in our previous comments to the panel and to the Agency, and we refer the SAB to those comments. One of us (SM) reviewed the draft in detail when it first appeared in 2011 and provided detailed written and oral comments to the Agency. In the comments below, we would like to raise two fundamental issues with the risk assessment as it stands, one procedural, and the other scientific. The procedural issue relates to the extremely limited manner in which public participation in the risk assessment process has been conducted to date. The scientific issue relates to an analysis of relevant data that EPA failed to provide to the public. The EPA was unwilling to release for analyses the full dataset with all covariates on which its risk assessment for non-cancer endpoints was based. The data were originally collected by the University of Cincinnati (Rohs et al., 2008). Under a FOIA request to the University of Cincinnati, we recently acquired and analyzed the data that forms the basis of the Agency's non-cancer risk assessment. We summarize the results here.

Procedural Issue

1. There was little opportunity for meaningful scientific dialogue with the panel during public meetings. We can understand that when a substantial number of individuals signs up to make comments, it is necessary to enforce a strict time limit on individual comments. However, this was not the situation at these panel meetings. At the discretion of the Chair and the Agency, it should have been possible for members of the public to engage in a meaningful scientific dialogue with the panel. We were denied that opportunity.
2. We understand that it is necessary to have multiple disciplines represented on the panel. However, the most controversial issues usually revolve around the interpretation of the analyses of dose-response data, particularly when these are epidemiologic data. This was clearly the case with this risk assessment for both the cancer and non-cancer endpoints. There were only two panel members who appeared to be comfortable with the more arcane statistical issues, and they were sharply divided in their scientific opinions. Clearly, the panelist who had serious problems with the Agency analyses chose not to submit a minority report. However, the panel report that the full committee is reviewing today purports to present a consensus that was never evident during the public discussions.

Scientific Issue

In a precedent-setting move, the Agency is proposing a reference concentration (RfC) for LAA based on a non-cancer endpoint. The proposed RfC for LAA, which will likely be applied to all forms of asbestos, is 0.00002 fibers/cc, which is below background levels of asbestos in many parts of the country. The Agency uses pleural plaques as the endpoint for derivation of the RfC, contending that pleural plaques are not just markers of asbestos exposure, but are adverse health effects associated with decrements in pulmonary function and other more serious conditions. We believe that this position has little scientific support as we have pointed out to the panel in our previous comments. We do not wish to re-argue this

issue here. We simply point out that the panel recommendations to the Agency on this matter contain serious factual inaccuracies that should be corrected. For example, for pulmonary function, the panel report refers to the American Thoracic Society 2004 report and recommends the addition of 3 additional references (Lilis 1991, Paris 2009, Clin 2011). Paris 2009 does not even discuss pulmonary function and Lilis 1991 is the ATS 2004 reference (112) in the following quote concerning plaques and FVC: "This has not been a consistent finding (110, 111) and longitudinal studies have not shown a more rapid decrement in pulmonary function in subjects with pleural plaques (112). Decrements, when they occur, are probably related to early subclinical fibrosis." The SAB panel specifically lists references used by the ATS 2004 report some of which are incorrect including some that were clearly published several years after the ATS report.

The derivation of this RfC is based on the prevalence of pleural plaques in a small sub-cohort of the full Rohs cohort. Whereas the full Rohs cohort consists of 280 subjects with 68 cases of pleural plaque, the sub-cohort on which EPA bases its RfC consists of 118 individuals with 12 pleural plaques. The table below shows the distribution of cases of pleural plaque in this sub-cohort by deciles of cumulative exposure. It is clear that there is little information in this sub-cohort for a proper dose-response analysis.

Decile	Exposure (f/cc-yr)	Cases	Subjects	Prevalence
1	0.02	1	12	0.08
2	0.04	0	12	0.00
3	0.07	1	12	0.08
4	0.09	0	12	0.00
5	0.11	0	11	0.00
6	0.14	1	12	0.08
7	0.22	2	12	0.17
8	0.32	2	12	0.17
9	0.50	1	12	0.08
10	2.29	4	11	0.36

Table 1: The sub-cohort used by the EPA for derivation of the RfC by deciles of exposure. The second column labeled "Exposure" is the average cumulative exposure in each decile. It is clear that any dose-response relationship is driven by the cases (number of individuals with plaque) in the highest decile.

We have analyzed both the sub-cohort used by the Agency and the full Rohs cohort. We present a brief summary of our findings here. These indicate clearly that the results in the sub-cohort are highly inconsistent with the results in the full cohort. These results indicate also that these data cannot be used for estimation of an RfC using the simplistic approach the Agency has adopted.

In both the full Rohs cohort and the sub-cohort, it is possible to perform dose-response analyses with three distinct measures of 'dose', cumulative exposure (ce), concentration, and duration of exposure.

1. The sub-cohort is too small to distinguish among models, with many models yielding virtually identical fits as judged by the Akaike Information Criterion (AIC). Nonetheless, the logistic regression model with concentration as the measure of 'dose' describes the data best as judged by the AIC, i.e., has the lowest AIC. Furthermore, concentration is the only measure of 'dose' that is statistically significant in these data. Despite this fact, the Agency has based its RfC on the Michaelis-Menten model with ce as the measure of 'dose'. With only 12 pleural plaques, the dataset is not large enough to test the impact of confounders, such as age and body mass index (BMI). The panel recommended that the EPA use the dichotomous Hill model with ce as the measure of exposure and with two parameters (the background and the plateau) fixed at highly uncertain values derived from epidemiologic studies. We have implemented this model and find that the logistic regression model with concentration as the measure of 'dose' describes the data as well as the constrained dichotomous Hill model. Thus, these data are too small to distinguish between the logistic regression model with concentration as a measure of 'dose' and the constrained dichotomous Hill model with ce as the measure of 'dose'. Clearly, these data should not be used for the estimation of an RfC. As noted below, however, when we analyzed the original Rohs data, which has far more pleural plaques than the sub-cohort (68 versus 12), the constrained dichotomous Hill model is resoundingly rejected.
2. In the full Rohs dataset, duration of exposure is by far the best measure of 'dose'. In fact, it is clear that the probability of pleural plaque is a function of both concentration and duration of exposure and, therefore, ce is a poor measure of 'dose'. Age is a strong confounder, with the coefficients for any of the measures of 'dose' becoming substantially attenuated when age is included in the regression model. Furthermore, the probability of plaque is a non-linear function of duration. The median duration of exposure in this cohort is about 25 years. With the data stratified on duration, there is no evidence of an association of any measure of 'dose' with probability of pleural plaques for durations of exposure less than 25 years. It is clear from these

analyses that there is no straight-forward way to estimate an RfC from these data. In fact, if there is no evidence of an association of exposure with probability of plaques for durations of less than 25 years, then the whole concept of a reference concentration needs to be reconsidered.

3. The constrained dichotomous Hill model recommended by the panel does a very poor job of fitting the full Rohs dataset.
4. Both the Agency and the panel appear to have lost sight of a fundamental fact. Since the point of departure (POD) is the lower 95% confidence limit on the benchmark dose (BMD), the greater the uncertainty in the data, the lower the POD. Therefore, in general, small data sets will lead to lower PODs than large datasets because the confidence interval on the BMD is inversely related to the size of the dataset. This is another important reason not to base RfCs on small datasets, such as the one used by the Agency in this risk assessment.

Recommendation

The full SAB should return this risk assessment for reconsideration by the panel.

APPENDIX B – 12

Statement for Public Teleconference for the SAB review of "Draft Toxicological Review of Libby Amphibole Asbestos" (EPA/635/r/002a)

Anatomical Considerations of Localized Pleural Thickenings (Pleural Plaques)

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May 1, 2012

ILO (2000) Definitions Incorrectly Used

- **EPA's draft Toxicological Review (August 2011) states that either of two conditions are recognized as LPT:**

"Pleural thickening: The pleural lining around the lungs (visceral pleura) and along the chest wall and diaphragm (parietal pleura) may thicken due to fibrosis and collagen deposits. Pleural thickening (all sites) is reported as either localized pleural thickening (LPT) or diffuse pleural thickening (DPT). DPT of the chest wall may be reported as in-profile or face on, and is recorded on the lateral chest wall "only in the presence of and in continuity with, an obliterated costophrenic angle" (ILO, 2000). Localized pleural thickening may also be viewed in-profile or face-on and is generally a pleural plaque (parietal). Calcification is noted where present (ILO, 2000)." (p. 5-15)

"Localized pleural thickening (LPT) viewed on a standard radiograph may include both pleural plaques and pleural thickening that does not involve blunting of the costophrenic angle (ILO, 2000). Thus, both parietal plaques and localized thickening of the visceral pleura may be designated as LPT." (p. 5-17)

"In summary, the radiographic classification of localized pleural thickening (LPT) under current ILO guidelines may include both parietal plaques (in the pleura lining the interior of the ribcage) and diffuse visceral thickening (without CPA obliteration) (ILO, 2000)." (p. 5-21)

ILO (2000) Definitions Incorrectly Used (Cont.)

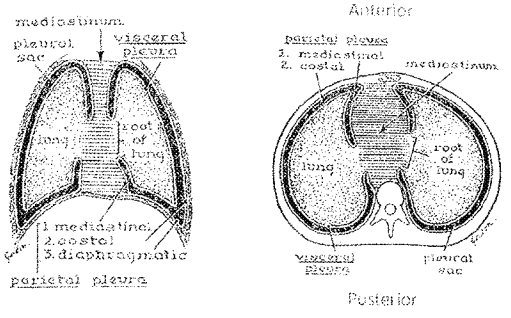
- ILO (2000) classifies as LPT as pleural plaques located in parietal pleura
- ILO states that the category of diffuse pleural thickening (DPT) requires 2 conditions:
  - (visceral) pleural thickening and costophrenic angle blunting.

"For the purpose of the ILO (2000) Classification, diffuse pleura thickening extending up the lateral chest wall is recorded *only* in the presence of, and in continuity with, an obliterated costophrenic angle." from ILO (2000)

ILO (2000) does not have a category of observations for diffuse pleural thickening without CPA obliteration.

Pleural Plaques (LPT) Do Not Displace Lung Tissue

- Pleural plaques (LPT) occur in the parietal pleura
- Parietal pleura does not touch lung tissue
- Pleural plaques (LPT) have small volumes



Pleural Plaques (LPT) Are Not a Critical Effect of Asbestos Exposure

- EPA defines Critical Effect as:
  - The first adverse effect, or its known precursor, that occurs as the dose rate of an agent increases (http://www.epa.gov/iris/help_gloss.htm#c viewed 4/17/12)

Pleural Plaques (LPT) are Not an Intermediate Stage in Progression to Neoplastic Disease

Pleural Plaques (LPT)	Tumors
Well-organized histologically	Lack of organization: chaotic
Connective tissue covered by epithelium	Composed of *either* epithelium (carcinomas) *or* connective tissues (sarcomas)
Oligocellular	High cellularity
Nonconfluent cells	Contiguous mass of cells
Minimal rate of mitosis	High rate of mitosis
Normal nuclei	Dysplastic or anaplastic nuclei
Extensive extracellular matrix	Small amount of extracellular material
Abundant collagen	Scarce collagen
Essentially avascular	Vascularity increased beyond typical amount for the tissue

APPENDIX B – 13

Libby Amphibole Asbestos Science Advisory Board
Panel Comments

1. Introduction

I have been the Medical Director of the Libby Medical Program (LMP) since January 2001 and as of March 2002 this has been my full time position up to the present time. Attached is a short summary of my professional background.

One of my primary responsibilities as the Medical Director of the LMP is to obtain peer review of chest x-rays and chest CT scans on people in Libby, Montana with asbestos exposure. This peer review process is done by board certified, academic chest radiologists, most of whom are members of the American College of Radiology Pneumoconiosis Committee.

In addition, medical records, pulmonary function tests, chest x-rays and CT scans are sent to pulmonologists for peer review in order to verify the existing diagnosis of previous asbestos exposure in LMP members. These pulmonologists are either practicing Montana or academic pulmonologists. These peer review processes have given me a clear insight and sound foundation as to the types of illness diagnosed in Libby, Montana.

As a physician, I am concerned that the risks associated with Libby Amphibole Asbestos (LAA) are accurately conveyed to the exposed population. I am most concerned that the draft report avoid either overstating or understating those risks, as both can have a potential adverse effect on patients, the health care system, and the broader community, especially with regard to the EPA clean-ups in Libby. I urge the SAB Panel to take this review very seriously with the understanding that many individuals will be living with the results and trying to assess how to apply them to their health care decisions.

2. Non-cancer endpoint: chest pain caused by pleural plaques

EPA's determination that chest pain caused by pleural plaques is an appropriate non-cancer endpoint is without support in the scientific literature.

EPA's chemical-specific charge question II.A.2 to the Science Advisory Board (SAB) requests that the SAB evaluate whether selection of localized pleural thickening (LPT), pleural plaques, as the non-cancer endpoint, on the basis that that condition is associated with restrictive pulmonary function and chronic chest pain, is scientifically supported. My review of the relevant scientific and medical evidence convinces me that it is not.

The draft report concludes that LPT should be used as "an adverse effect and an appropriate endpoint for RfC derivation" P. 5-21. As a physician and based upon my experience with the Libby community and health records subject to peer review at the LMP, I perceived this conclusion as both novel and unsupported.

The draft report summary paragraph, page 5 -21, avoids using the term pleural plaques and instead uses localized pleural thickening (LPT) whereas in fact they both mean the same thing. See ILO 2000 Revised guidelines. In addition, the term pleural lesions is

substituted for pleural plaques without any explanation, justification or reference. Because the draft goes on to state that pleural plaques are not statistically associated with decreased pulmonary function (see draft report at page 2, line 26 and 27), there is no sound scientific basis to conclude that LPT causes decreased lung function.

After review of the discussion in the draft report and cited literature, I want to share the following additional findings with the SAB Panel because the discussion contains a number of fundamental scientific flaws and goes directly to the charge question referenced above that this panel has been asked to address. Overall, the report's basis for using pleural plaques as a non-cancer end point is not supported by the references used in the draft. Moreover, these references do not support – and may even contradict - the statements for which they are cited. This error in the use of scientific literature is particularly disturbing where, as here, the authors are using the literature to support an important unprecedented principle that can have broad influence and wide-ranging policy implications.

a. ***The draft report provides no scientific support for its unwarranted assertion that pleural plaques have ragged irregular edges inducing irritation.***

First, the draft report inaccurately describes pleural plaques as having ragged and irregular edges instead of a smooth surface with sharply circumscribed borders. This statement is pertinent because of an inference that the ragged edges cause pain in sensitive lung issue.

As discussed below, the report lacks medical evidence for the hypotheses that pleural plaques have ragged and irregular edges that can irritate the pleura, which in turn, could cause constricting chest pain and loss of pulmonary function. Overall, the use of localized pleural plaques as an endpoint for RfC derivation would be contrary to the medical literature and a significant error. It is important to correct this error because of the potential health care implications for the Libby community. For example, it would be confusing and potentially harmful for angina or other constrictive chest pain to be misdiagnosed as pleural pain from previous asbestos exposure.

The draft at pages 5-18 and 5-21 addresses the unsupported premise that pleural plaques induce constricting chest pain. The discussion on pages 5-18 begins as follows:

> "Costal parietal plaques occur between the thoracic cage and parietal pleura, which is normally adherent to the thoracic cage (ATS, 2004: Jones, 2002). Costal parietal plaques have been described as collagen deposits with ragged irregular edges and up to 1 cm in depth and may be calcified."

Moreover, the statement is contrary to the scientific literature. In his lung pathology book, Dr. Andrew Churg describes parietal pleural plaques as follows: "Individual lesions may be completely smooth surfaced and flat, or they may be composed of small rounded knobs or both".

In another pathology book, Dr. Donald Greenberg states: "Grossly, the parietal plaques are elevated, firm, and glistening and have shapely circumscribed borders". He continues: "These ivory-colored structures may have either a smooth surface or a knobby appearance, consisting of multiple 5 mm nodules that create a candle wax dripping appearance".

Neither lung pathologist states pleural plaques have "ragged irregular edges." In fact, the pathology literature states the opposite. References supporting this conclusion include the following:

- Pathology of Occupational Lung Disease: Andrew Churg, M.D. and Francis H. Y. Green, M.D. 1988, page 241

- Pathology of Asbestos — Associated Diseases: Victor L. Roggli, S. Donald Greenberg and Phillip C. Pratt 1992, page 169

b. ***There is no scientific support for the assertion that pleural plaques induce chest pain.***

The draft report also lacks any scientific support for the assertion that pleural plaques are associated with chest pain. In support of that alleged association, page 5 – 18 of the draft report states that "These parietal plaques have been associated with constricting pain in the thoracic cavity (Mukherjee et al,, 2000; Bourbeau et al., 1990)." However, the cited references (Mukherjee and Bourbeau) do not support the proposition for which they are cited.

The first reference, Mukherjee et al., 2000, is a study of 1280 subjects from Wittenoom, Western Australia who were exposed to crocidolite asbestos. The subjects completed the Rose questionnaire on chest pain and 556 subjects (43%) experienced some chest pain. The type of pain was separated into non-anginal pain and anginal pain. The non-anginal pain was associated with parenchymal disease only. In other words, pleural plaques were not associated with non-anginal pain. Anginal pain was associated with pleural and parenchymal abnormalities. However, the source of anginal pain is the heart, not the pleura. This reference indicates non-cardiac pain is not caused by pleural plaques. Therefore, the Mukherjee study results not only fail to support the assertion in the draft report, but actually conflict with the text of the report. It is worth noting as well that the Mukherjee study is not included in the "References" (Section 7 of the draft report).

In addition, a paragraph on page 5-18 of the report states as follows:

"The parietal pleura is well innervated by the intercostal and phrenic nerves and is considered very sensitive to painful stimuli (Jones, 2002). With respect to parietal plaques, pain during exertion or exercise could result in restrained chest wall motion during exertion or exercise (Bourbeau et al., 1990). Thus, Bourbeau et al., (1990) hypothesized that the dyspnea and changes in pulmonary function noted in individuals with pleural plaques may be due to physical irritation and perhaps a constricting action where parietal plaques are well progressed or numerous and impact a large proportion of the parietal surface."

In Bourbeau et al., 1990, there is no mention of physical irritation (pain) during exertion or exercise resulting in restrained chest wall motion and a constricting action leading to dyspnea and changes in pulmonary function. Thus, this hypothesis regarding physical pain is also unsupported by the cited scientific literature.

In summary, neither cited reference supports the contention that pleural plaques cause chest pain. In fact, one of the references suggests the opposite: that pleural plaques do not cause chest pain.

c. *The ILO Revised 2000 Guidelines are incorrectly interpreted and mis-quoted in support of the proposition that "localized visceral thickening" causes chest pain*

The summary paragraph on page 5-21 of the draft report begins as follows:

"In summary, the radiographic classification of localized pleural thickening (LPT) under current ILO guidelines may include both parietal plaques (in the pleura lining the interior of the ribcage) and diffuse visceral thickening (without CPA obliteration) (ILO, 2000). The two lesions (parietal plaques and localized visceral thickening) are distinct and may contribute independently to observed health effects. Parietal plaques are known to induce chronic constricting chest pain that increases in severity as the extent of the plaques increases."

The ILO guidelines indicate that diagnosing visceral pleural thickening (VPT) on a single PA chest x-ray is unreliable. In addition, the guidelines do not separate VPT into diffuse visceral thickening and localized visceral thickening as the draft report does. The attempt of the report to do so is unfounded science which does not follow the ILO guidelines and only serves to mislead and confuse the reader. No scientific basis exists to conclude that localized visceral thickening contributes to untoward health effects.

The Revised ILO 2000 Guidelines state the following at page7:

- ✓ "Diffuse pleural thickening historically has referred to thickening of the visceral pleura. The radiological distinction between parietal and visceral pleural thickening is not always possible on a postero-anterior radiograph."

- ✓ "For the purpose of the ILO (2000) Classification, diffuse pleural thickening extending up the lateral chest wall is recorded *only* in the presence of, and in continuity with, an obliterated costophrenic angle."

Except for the above passing reference to "visceral pleural thickening", the ILO 2000 guidelines have no discussion or mention of diffuse visceral thickening. No scientific basis exists for the draft report to conclude or imply that visceral pleural thickening is a separate condition from pleural plaques and a cause of morbidity.

In sum, the statement that "Parietal plaques are known to induce chronic constricting chest pain that increases in severity as the extent of the plaques increases" (p. 5-21) is not supported by any cited scientific reference. Instead of demonstrating that localized pleural plaques cause chest pain, the scientific literature supports the opposite hypothesis: that pleural plaques do not cause chest pain. The following references support this view point:

- "Broderick A, Fuortes LI Merchant JA, Galvin JR, Schwartz DA. Pleural determinants of restrictive lung function and respiratory symptoms in an asbestos-exposed population, Chest 1992; 101: 684-691.

- Jarvholm B, Larsson S. Do pleural plaques produce symptoms? A brief report. J Occup Med 1988; 30: 345-347

- Sutapa Mukherjee, Nicholas de Klerk, Lyle J. Palmer, N. J. Olsen, S. C. Pang, and A. William Musk. Chest Pain in Asbestos-exposed Individuals with Benign

Pleural and Parenchymal Disease. Am. J. Respir. Crit. Care Med., Volume 162, Number 5, November 2000, 1807-1811

To my knowledge, this draft proposes, for the first time, that a non-cancer endpoint be established for asbestos exposure on the basis that pleural plaques cause chest pain. This is a significant new endeavor with potentially broad ramifications. If undertaken, it should be supported by generally accepted medical principles and findings, as well as sound science. That support is not present in the draft report. As a result, the SAB should recommend to EPA, in response to charge question II.A.2, that EPA remove from the draft report chest pain caused by pleural plaques as a non-cancer end point.

3. **Tremolite asbestos compared to LAA**

The draft report inappropriately attributes to LAA the toxicity associated with tremolite asbestos. The draft report presents studies which deal with a single form of amphibole asbestos (tremolite) and inappropriately implies that those studies reflect the toxicity of LAA. This comparison inaccurately applies those data.

Tremolite asbestos should not be confused with LAA. Since the composition and characteristics of the two are different, literature regarding tremolite asbestos cannot be applied directly to LAA.

In section 4.2 **(sub-chronic and chronic studies and cancer bioassays in animals oral inhalation and other routes of exposure),** the hypothesis is made that studies using pure tremolite will help "to potentially increase understanding of the effects and mechanisms of Libby amphibole asbestos". This statement is based on the following assumptions:

- "Tremolite is an amphibole asbestos fiber that is a component of Libby Amphibole asbestos (-6%)"
- "In early studies Libby Amphibole asbestos was defined as tremolite."

According to Meeker's publication in 2003, the Libby Amphiboles are composed primarily of winchite 84% and richterite 11%, with only approximately 6% tremolite. (see External Review draft, page 2-14). As a result, studies assessing the toxic effects of tremolite asbestos can not properly be employed, as a matter of sound science, to evaluate the effects of LAA. For example, Table 4-16 (at pages 4-52 and 4-53 of the draft report), "In vivo data following exposure to tremolite asbestos," summarizes nine animal studies (7 rats, 1 mouse and 1 hamster) in which pure tremolite is administered. The toxic effects in these studies should not be compared to LAA, which is only 6% tremolite. None of the studies themselves directly compares tremolite to LAA.

The SAB should advise EPA to make clear that the toxic effects of pure tremolite are not the same as the toxic effects of LAA, and can not properly be used to evaluate the toxic effects of LAA.

4. **In vitro comparison studies**

The risk assessment should recognize and accurately interpret comparative studies that correlate LAA with other amphiboles and apply the information that these studies yield.

Table 4-18, at page 4-63 of the draft report, summarizes six published studies that directly compare LAA with other amphibole asbestos, either crocidolite or amosite. In all these studies, the LAA is less reactive or causes less DNA and gene damage when compared to crocidolite or amosite. The significance of this table is obscured because of the misleading title of the Table: "In vitro data following exposure to Libby Amphibole asbestos." To avoid confusion and enhance transparency, the report should acknowledge that all available scientific studies that compare LAA to other amphibole asbestos conclude that LAA is less toxic and reactive than other amphibole asbestos.

The SAB should recommend to EPA the following:

- Change the title of Table 4-18 to "In vitro data comparing LAA with other amphibole asbestos."
- Conclude this section by stating: "In all studies that compare the reactivity and toxicity of LAA with other amphibole asbestos, the LAA is less reactive and less toxic."

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Attachment 1

Professional Background

- Board certified in internal medicine and nephrology
- 1970 — 1972 Major United States Army
  - 1970 — 1971 Physician, Brooke Army Medical Center, San Antonio, Texas
  - 1971 — 1972 Commanding Officer, US Army Hemodialysis Unit Saigon, Vietnam
- 1972 — 1996 Practiced internal medicine and nephrology at Monmouth Medical Center (MMC), Long Branch, New Jersey. MMC is a 450 bed hospital with a medical school affiliation and residency programs
- 1997 --1998 Medical Director of VRG International, a contract research organization (CRO), which conducted clinical trials for major pharmaceutical companies
- 1999 — 2000 Medical Director of Wellspring Pharmaceutical Company
- 2001 to present Medical Director of the Libby Medical Program

Attachment 2

References Cited

1. Sutapa Mukherjee, Nicholas de Klerk, Lyle J. Palmer, N. J. Olsen, S. C. Pang, and A. William Musk. Chest Pain in Asbestos-exposed Individuals with Benign Pleural and Parenchymal Disease. Am. J. Respir. Crit. Care Med., Volume 162, Number 5, November 2000, 1807-1811

2. Bourbeau, J. Ernst, P. Chrome, J. Armstrong B.and Becklake, M (1990) The relationship between respiratory impairment and asbestos-related pleural abnormalities in an active work force. AM Rev Respir Dis 142:837-842

3. Broderick A, Fuortes LJ Merchant JA, Galvin JR, Schwartz DA. Pleural determinants of restrictive lung function and respiratory symptoms in an asbestos-exposed population. Chest 1992; 101: 684-691.

4. Jarvholm B, Larsson S. Do pleural plaques produce symptoms? A brief report. J Occup Med 1988; 30: 345-347

APPENDIX B – 14

Comments for EPA and SAB Regarding Libby Amphibole Asbestos

Submitted by Dr. Jay Flynn
April 17th, 2012

Thank you for making available the SAB Panels' deliberative draft report, dated April 11, 2012 (Panel's Draft Report). While I reiterate my previously presented comments and concerns, I wanted to take this opportunity to address a new issue reflected in the Panel's draft report. I concur with the SAB Panels' observation that "additional analyses/cohorts are needed to strengthen and support the RfC." However, I suggest that the SAB Panel reconsider and remove any suggestion that the EPA use a recent Larson paper that uses the ATSDR data from Libby, Montana, 2000 and 2001, for assessing pleural abnormalities among the Libby participants.

At issue is the scientific validity of the following paper: **Associations between radiographic findings and spirometry in a community exposed to Libby amphibole;** Theodore C Larson, [1] Michael Lewin, [1] E. Brigitte Gottschall, [2] Vinicius C Antao, [1] Vikas Kapil, [3] Cecile S Rose[2] which was published online March 1st, 2012 in the Journal of Occupational and Environmental Medicine. This paper has not yet been published in the Journal itself and will be referenced in this report as the Larson paper.

Due to the following significant problems with this paper and underlying data deficiencies as discussed below, the paper should not assist the EPA in deriving the non-cancer endpoint. In addition, as pointed out in my comments herein, there are significant questions as to whether radiographic evidence of localized pleural thickening (LPT) in humans is scientifically sufficient for derivation of the RfC. I recommend that the SAB Panel reconsider its preliminary assessment of that issue as reflected in the Panel's Draft Report, in light of the limited reliability of this radiographic evidence.

1. **Larson's Study Used Data that Failed to Distinguish Between Plueral Abnormalities and Other Innocuous Observations.**

Larson used the ATSDR data that grouped together in one category all readings from < 1 to 5 mm in width, but only those that are greater than 2 mm in width are defined under the Larson's methodology as pleural abnormalities. Thus the use of readings of less than 2 mm in width biases the data.

As background, the ATSDR B readers in 2000 and 2001 followed the 1980 ILO Guidelines when interpreting Posterior / Anterior PA Chest X-Rays. Under these 1980 guidelines, the threshold required to identify the thickness of any pleural abnormality was not specified. Thus the B reader had discretion to determine whether a pleural abnormality existed. The 1980 ILO guidelines used by the ATSDR B readers do not have a minimal thickness for reading a pleural abnormality so that the B readers could read any minimal pleural thickening, including pleural fat, as an abnormality.

In the ATSDR data, category "A" reflects all observations that fell within a range of 0 to 5 mm. There is no way to determine which of the X-Rays reflected observations of less than 2 mm. The

Larson paper adapts this ATSDR data, including the determinations from the ATSDR B Readers for use in their 2012 analysis.

In 1990 Bourbeau et al realized a minimal thickness for reading pleural plaques on a chest x-ray by B readers needed to be established. The 1980 ILO Guidelines used by the ATSDR B readers were flawed and outdated. To address this, the Bourbeau model established a minimal threshold of 2mm for pleural abnormalities. Later, further addressing this deficiency in 2000 the ILO established the minimal thickness for reading a pleural plaque at about 3mm in the Revised Edition 2000 of the ILO guidelines, published in 2002.

Simply put: the model and the data are incompatible. The Larson paper uses the Bourbeau model to develop index scores of pleural thickening and the Bourbeau model is incompatible with the ATSDR data. The Bourbeau model establishes a minimal threshold of 2mm for pleural abnormalities. As described above, the ATSDR data applied the 1980 guidelines, so it had no minimal threshold. The Larson paper used the Category A readings from the ATSDR data (encompassing readings within a range of 0 to 5 mm) and applied a scoring system designed only for readings of at least 2 mm. Since these two systems are mis-matched they never should have been used together, making the data flawed and the paper invalid.

Bear in mind, Larson's results were in the very low range of the scoring system 0-24. Modest was a score of <2.5 for LPT and high = or >2.5. The median value for all subjects with LPT was only 2.5. At this low range, minimal degrees of thickness become important especially with the B readers having no minimal threshold to read an abnormality.

- The Bourbeau et al paper uses only one B reader because "one reader was selected prior because a previous study indicated that he achieved better reproducibility for reading of pleural abnormality." The Larson paper had to depend on two or three B readers to detect a pleural abnormality because this was how the ATSDR medical testing study for Libby, Montana was designed. Bourbeau et al do not specify how the pleural abnormalities identified by multiple B readers should be tabulated. Larson states 708 had circumscribed pleural plaques indentified by at least 2 B readers, but does not state how the index scores were derived or what the range of the index scores was. Were the individual scores averaged for only those with positive reads or were the negative B reader reports also included in the averaging?. Including the negative reports when tabulating the index scores could result in a significant lowering of the mean score of 2.5.

- The methodology designed by Bourbeau et al was developed for their research and publications. This has never been validated and accepted by the world wide scientific community.

  The Bourbeau et al Assessment of Pleural Abnormality scoring system for chest wall pleural thickening is not recognized by:

  - The American College of Radiology Pneumoconiosis Committee
  - The American Thoracic Society
  - The American College of Chest Physicians